



(11) **EP 2 865 765 A1**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
29.04.2015 Bulletin 2015/18

(51) Int Cl.:
C12Q 1/68 (2006.01)

(21) Application number: **14174637.0**

(22) Date of filing: **19.04.2011**

(84) Designated Contracting States:
**AL AT BE BG CH CY CZ DE DK EE ES FI FR GB
GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO
PL PT RO RS SE SI SK SM TR**

(30) Priority: **20.04.2010 US 326043 P**
20.04.2010 EP 10004190
01.10.2010 EP 10185136

(62) Document number(s) of the earlier application(s) in
accordance with Art. 76 EPC:
11715666.1 / 2 561 091

(71) Applicant: **Comprehensive Biomarker Center
GmbH**
69120 Heidelberg (DE)

(72) Inventors:
• **Keller, Andreas**
66346 Püttlingen (DE)

- **Stähler, Peer**
68167 Mannheim (DE)
- **Beier, Markus**
69469 Weinheim (DE)
- **Meder, Benjamin**
69221 Dossenheim (DE)
- **Katus, Hugo**
69120 Heidelberg (DE)
- **Rottbauer, Wolfgang**
89075 Ulm (DE)

(74) Representative: **Geling, Andrea**
ZSP Patentanwälte
Partnerschaftsgesellschaft
Radtkoferstrasse 2
81373 München (DE)

Remarks:

This application was filed on 27-06-2014 as a
divisional application to the application mentioned
under INID code 62.

(54) **Complex miRNA sets as novel biomarkers for an acute coronary syndrome**

(57) The present invention relates to single polynucleotides or sets of polynucleotides for detecting single miRNAs or sets of miRNAs for diagnosing and/or prognosing of an acute coronary syndrome in a blood sample from a human. Further, the present invention relates to means for diagnosing and/or prognosing of an acute coronary syndrome comprising said polynucleotides or sets of polynucleotides. Furthermore, the present invention relates to a method for diagnosing and/or prognosing of

an acute coronary syndrome based on the determination of expression profiles of single miRNAs or sets of miRNAs representative for an acute coronary syndrome compared to a reference. In addition, the present invention relates to a kit for diagnosing and/or prognosing of an acute coronary syndrome comprising means for determining expression profiles of single miRNAs or sets of miRNAs representative for an acute coronary syndrome and at least one reference.

EP 2 865 765 A1

Description

TECHNICAL FIELD OF INVENTION

[0001] The present invention relates to single polynucleotides or sets of polynucleotides for detecting single miRNAs or sets of miRNAs for diagnosing and/or prognosing of an acute coronary syndrome in a blood sample from a human. Further, the present invention relates to means for diagnosing and/or prognosing of an acute coronary syndrome comprising said polynucleotides or sets of polynucleotides. Furthermore, the present invention relates to a method for diagnosing and/or prognosing of an acute coronary syndrome based on the determination of expression profiles of single miRNAs or sets of miRNAs representative for an acute coronary syndrome compared to a reference. In addition, the present invention relates to a kit for diagnosing and/or prognosing of an acute coronary syndrome comprising means for determining expression profiles of single miRNAs or sets of miRNAs representative for an acute coronary syndrome and at least one reference.

BACKGROUND OF THE INVENTION

[0002] Today, biomarkers play a key role in early diagnosis, risk stratification, and therapeutic management of cardiac diseases such as acute myocardial infarction (AMI) and heart failure [10-13]. Established biomarkers such as the cardiac troponins and b-type natriuretic peptides were mainly discovered by candidate approach [13, 14]. By contrast, the recent development of high-throughput molecular technologies that allow with a reasonable effort the analysis of whole transcriptomes, proteomes, and metabolomes of individuals at risk, may lead to the discovery of novel biomarkers in an unbiased approach [15, 16].

[0003] MicroRNAs (miRNAs) are a new class of biomarkers. They represent a group of regulatory elements that enable cells to fine-tune complex gene expression cascades in a wide range of biological processes, such as proliferation, differentiation, apoptosis, stress-response, and oncogenesis [1-7]. In the cardiovascular system, miRNAs are not only important for heart and vascular development, but also play an essential role in cardiac pathophysiology, such as hypertrophy, arrhythmia, and ischemia [8, 9]. Particularly, miRNAs are important regulators of adaptive and maladaptive responses in cardiovascular diseases and hence are considered to be potential therapeutic targets.

[0004] Since recently it is known that miRNAs are not only present in tissues but also in human blood both as free circulating nucleic acids and in mononuclear cells. This may be due to the fact that miRNAs expressed in diverse tissues or cells may be able to be released into circulating blood. Although the mechanism why miRNAs are found in human blood is not fully understood yet, this finding makes miRNAs to biological markers for diagnostics for various types of diseases based on blood analysis including acute coronary syndrome or hypertrophic cardiomyopathy. For example, Ai et. al (Biochem. and Biophysical Research Communication, 2010, 391, 73-77) report that miRNAs are novel biomarkers for early diagnosis of acute myocardial infarction in plasma of humans. Expression levels of hsa-miR-1, hsa-miR-133a, hsa-miR-499 and hsa-miR-208a were found higher in subjects with acute myocardial infarction in comparison to healthy persons, patients with non-AMI coronary heart disease or patients with other cardiovascular diseases. Further, Wang et al. (European Heart Journal, 2010, 31, 659-666) found that the expression level of hsa-miR-1 was higher in plasma from human AMI patients compared with non-AMI subjects.

[0005] Thus, various miRNA markers have been proposed to indicate heart and cardiovascular system diseases. However, many of these markers have shortcomings such as reduced sensitivity, not sufficient specificity or do not allow timely diagnosis. Accordingly, there is still a need for novel and efficient miRNAs or sets of miRNAs as markers, effective methods and kits for the diagnosis of said diseases. Particularly, the potential role of miRNAs present in human blood as biomarkers for the diagnosis of heart and cardiovascular diseases has not been systematically evaluated yet.

[0006] The inventors of the present invention assessed for the first time the expression of miRNAs on a whole-genome level in patients with acute myocardial infarction (AMI). They identified novel miRNAs which are significantly dysregulated in blood of AMI patients in comparison to healthy controls. Said miRNAs predict AMI with high specificity and sensitivity. The inventors of the present invention also pursued a multiple biomarker strategy to circumvent the above-mentioned limitations by adding accuracy and predictive power. In detail, by using a machine learning algorithm, they identified unique miRNA signatures that predict diagnosis of AMI with even higher power, indicating that both, single miRNAs and especially complex miRNA signatures or sets derived from human blood can be used as novel biomarkers. The inventors of the present invention further found that some other single miRNAs directly correlate with heart infarct size estimated by Troponin T release.

SUMMARY OF THE INVENTION

[0007] In a first aspect, the invention provides a polynucleotide for detecting a miRNA or a set comprising at least two polynucleotides for detecting a set comprising at least two miRNAs for diagnosing and/or prognosing of an acute coronary

syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283.

[0008] In a second aspect, the invention provides a method for diagnosing and/or prognosing of an acute coronary syndrome comprising the steps of:

- (i) determining an expression profile of a miRNA or a set comprising at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, a fragment thereof, and a sequence having at least 80% sequence identity thereto, and
- (ii) comparing said expression profile to a reference, wherein the comparison of said expression profile to said reference allows for the diagnosis and/or prognosis of an acute coronary syndrome and/or applying an algorithm or a mathematical function to said expression profile, wherein the application of said algorithm or mathematical function to said expression profile allows for the diagnosis and/or prognosis of an acute coronary syndrome.

[0009] In a third aspect, the invention provides means for diagnosing and/or prognosing of an acute coronary syndrome comprising a polynucleotide or a set comprising at least two polynucleotides according to the first aspect.

[0010] In a fourth aspect, the invention provides a kit for diagnosing and/or prognosing of an acute coronary syndrome comprising

- (i) means for determining an expression profile of a miRNA or a set comprising at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, a fragment thereof, and a sequence having at least 80% sequence identity thereto; and
- (ii) at least one reference and/or algorithm or mathematical function, preferably comprised on at least one data carrier.

[0011] This summary of the invention does not necessarily describe all features of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0012] Before the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

[0013] In the following, the elements of the present invention will be described. These elements are listed with specific embodiments, however, it should be understood that they may be combined in any manner and in any number to create additional embodiments. The variously described examples and preferred embodiments should not be construed to limit the present invention to only the explicitly described embodiments. This description should be understood to support and encompass embodiments which combine the explicitly described embodiments with any number of the disclosed and/or preferred elements. Furthermore, any permutations and combinations of all described elements in this application should be considered disclosed by the description of the present application unless the context indicates otherwise.

[0014] Preferably, the terms used herein are defined as described in "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", H.G.W. Leuenberger, B. Nagel, and H. Kölbl, Eds., Helvetica Chimica Acta, CH-4010 Basel, Switzerland, (1995).

[0015] To practice the present invention, unless otherwise indicated, conventional methods of chemistry, biochemistry, and recombinant DNA techniques are employed which are explained in the literature in the field (cf., e.g., Molecular Cloning: A Laboratory Manual, 2nd Edition, J. Sambrook et al. eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor 1989).

[0016] Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, etc.), whether *supra* or *infra*, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[0017] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[0018] As used in this specification and in the appended claims, the singular forms "a", "an", and "the" include plural referents, unless the content clearly dictates otherwise. For example, the term "a test compound" also includes "test compounds".

[0019] The terms "microRNA" or "miRNA" refer to single-stranded RNA molecules of at least 10 nucleotides and of not more than 35 nucleotides covalently linked together. Preferably, the polynucleotides of the present invention are molecules of 10 to 33 nucleotides or 15 to 30 nucleotides in length, more preferably of 16 to 28 nucleotides or 17 to 27 nucleotides in length, i.e. 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 nucleotides in length, not including optionally labels and/or elongated sequences (e.g. biotin stretches). The miRNAs regulate gene expression and are encoded by genes from whose DNA they are transcribed but miRNAs are not translated into protein (i.e. miRNAs are noncoding RNAs). The genes encoding miRNAs are longer than the processed mature miRNA molecules. The miRNAs are first transcribed as primary transcripts or pri-miRNAs with a cap and poly-A tail and processed to short, 70 nucleotide stem-loop structures known as pre-miRNAs in the cell nucleus. This processing is performed in animals by a protein complex known as the Microprocessor complex consisting of the nuclease Drosha and the doublestranded RNA binding protein Pasha. These pre-miRNAs are then processed to mature miRNAs in the cytoplasm by interaction with the endonuclease Dicer, which also initiates the formation of the RNA-induced silencing complex (RISC). When Dicer cleaves the pre-miRNA stem-loop, two complementary short RNA molecules are formed, but only one is integrated into the RISC. This strand is known as the guide strand and is selected by the argonaute protein, the catalytically active RNase in the RISC, on the basis of the stability of the 5' end. The remaining strand, known as the miRNA*, anti-guide (anti-strand), or passenger strand, is degraded as a RISC substrate. Therefore, the miRNA*s are derived from the same hairpin structure like the "normal" miRNAs. So if the "normal" miRNA is then later called the "mature miRNA" or "guide strand", the miRNA* is the "anti-guide strand" or "passenger strand".

[0020] The terms "microRNA*" or "miRNA*" refer to single-stranded RNA molecules of at least 10 nucleotides and of not more than 35 nucleotides covalently linked together. Preferably, the polynucleotides of the present invention are molecules of 10 to 33 nucleotides or 15 to 30 nucleotides in length, more preferably of 16 to 28 nucleotides or 18 to 23 nucleotides in length, i.e. 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 nucleotides in length, not including optionally labels and/or elongated sequences (e.g. biotin stretches). The "miRNA*s", also known as the "anti-guide strands" or "passenger strands", are mostly complementary to the "mature miRNAs" or "guide strands", but have usually single-stranded overhangs on each end. There are usually one or more mismatches and there are sometimes extra or missing bases causing single-stranded "bubbles". The miRNA*s are likely to act in a regulatory fashion as the miRNAs (see also above). In the context of the present invention, the terms "miRNA" and "miRNA*" are interchangeable used.

[0021] The term "miRBase" refers to a well established repository of validated miRNAs. The miRBase (www.mirbase.org) is a searchable database of published miRNA sequences and annotation. Each entry in the miRBase Sequence database represents a predicted hairpin portion of a miRNA transcript (termed mir in the database), with information on the location and sequence of the mature miRNA sequence (termed miR). Both hairpin and mature sequences are available for searching and browsing, and entries can also be retrieved by name, keyword, references and annotation. All sequence and annotation data are also available for download. The sequences of the miRNAs for diagnosis and/or prognosis of an acute coronary syndrome (AMI) listed in Figure 12 are based on miRBase version 14.0.

[0022] As used herein, the term "nucleotides" refers to structural components, or building blocks, of DNA and RNA. Nucleotides consist of a base (one of four chemicals: adenine, thymine, guanine, and cytosine) plus a molecule of sugar and one of phosphoric acid. The term "nucleosides" refers to glycosylamine consisting of a nucleobase (often referred to simply base) bound to a ribose or deoxyribose sugar. Examples of nucleosides include cytidine, uridine, adenosine, guanosine, thymidine and inosine. Nucleosides can be phosphorylated by specific kinases in the cell on the sugar's primary alcohol group (-CH₂-OH), producing nucleotides, which are the molecular building blocks of DNA and RNA.

[0023] The term "polynucleotide", as used herein, means a molecule of at least 10 nucleotides and of not more than 35 nucleotides covalently linked together. Preferably, the polynucleotides of the present invention are molecules of 10 to 33 nucleotides or 15 to 30 nucleotides in length, more preferably of 16 to 28 nucleotides or 17 to 27 nucleotides in length, i.e. 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 nucleotides in length, not including optionally spacer elements and/or elongation elements described below. The depiction of a single strand of a polynucleotide also defines the sequence of the complementary strand. Polynucleotides may be single stranded or double stranded, or may contain portions of both double stranded and single stranded sequences. The term "polynucleotide" means a polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and RNA molecules, both sense and anti-sense strands. In detail, the polynucleotide may be DNA, both cDNA and genomic DNA, RNA, cRNA or a hybrid, where the polynucleotide sequence may contain combinations of deoxyribonucleotide or ribonucleotide bases, and combinations of bases including uracil, adenine, thymine, cytosine, guanine, inosine, xanthine, hypoxanthine, isocytosine and isoguanine. Polynucleotides may be obtained by chemical synthesis methods or by recombinant methods.

[0024] In the context of the present invention, a polynucleotide as a single polynucleotide strand provides a probe

(e.g. miRNA capture probe) that is capable of binding to, hybridizing with, or detecting a target of complementary sequence, such as a nucleotide sequence of a miRNA or miRNA*, through one or more types of chemical bonds, usually through complementary base pairing, usually through hydrogen bond formation. Polynucleotides in their function as probes may bind target sequences, such as nucleotide sequences of miRNAs or miRNAs*, lacking complete complementarity with the polynucleotide sequences depending upon the stringency of the hybridization condition. There may be any number of base pair mismatches which will interfere with hybridization between the target sequence, such as a nucleotide sequence of a miRNA or miRNA*, and the single stranded polynucleotide described herein. However, if the number of mutations is so great that no hybridization can occur under even the least stringent hybridization conditions, the sequences are no complementary sequences. The polynucleotide variants including polynucleotide fragments or polynucleotide mutants and the miRNA variants including miRNA fragments or miRNA mutants are further defined below. The present invention encompasses polynucleotides in form of single polynucleotide strands as probes for binding to, hybridizing with or detecting complementary sequences of miRNAs (target), which are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, particularly of SEQ ID NO: 1 to SEQ ID NO: 241.

[0025] The polynucleotide, e.g. the polynucleotide used as a probe for detecting a miRNA or miRNA*, may be unlabeled, directly labeled, or indirectly labeled, such as with biotin to which a streptavidin complex may later bind. The polynucleotide, e.g. the polynucleotide used as a probe for detecting a miRNA or miRNA*, may also be modified, e.g. may comprise an elongation (EL) element. For use in a RAKE or MPEA assay as shown in Figures 10 and 11, a polynucleotide with an elongation element may be used as a probe. The elongation element comprises a nucleotide sequence with 1 to 30 nucleotides chosen on the basis of showing low complementarity to potential target sequences, such as nucleotide sequences of miRNAs or miRNAs*, therefore resulting in not to low degree of cross-hybridization to a target mixture. Preferred is a homomeric sequence stretch N_n with $n = 1$ to 30, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, and $N = A$ or C , or T or G . Particularly preferred is a homomeric sequence stretch N_n with $n = 1$ to 12, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, and $N = A$ or C , or T or G . The polynucleotide, e.g. the polynucleotide used as a probe for detecting a miRNA or miRNA*, may be present in form of a tandem (Figure 9), i.e. in form of a polynucleotide hybrid of two different or identical polynucleotides, both in the same orientation, i.e. 5' to 3' or 3' to 5', or in different orientation, i.e. 5' to 3' and 3' to 5'. Said polynucleotide hybrid/tandem may comprise a spacer element. For use in a tandem hybridization assay as shown in Figure 9, the polynucleotide hybrid/tandem as a probe may comprise a spacer (SP) element. The spacer element represents a nucleotide sequence with $n = 0$ to 12, i.e. 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, nucleotides chosen on the basis of showing low complementarity to potential target sequences, such as nucleotide sequences of miRNAs or anti-miRNAs, therefore resulting in not to low degree of cross-hybridization to a target mixture. It is preferred that n is 0, i.e. that there is no spacer between the two miRNA sequence stretches.

[0026] For detection purposes, the miRNA(s) or miRNA*(s) may be employed unlabeled (Figures 10, 11), directly labeled, or indirectly labeled (Figures 8, 9), such as with biotin to which a streptavidin complex may later bind.

[0027] The term "label", as used herein, means a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. For example, useful labels include ^{32}P , fluorescent dyes, electron-dense reagents, enzymes (e.g., as commonly used in an ELISA), biotin, digoxigenin, or haptens and other entities which can be made detectable. A label may be incorporated into nucleic acids at any position, e.g. at the 3' or 5' end or internally. The polynucleotide for detecting a miRNA (polynucleotide probe) and/or the miRNA itself may be labeled.

[0028] The term "stringent hybridization conditions", as used herein, means conditions under which a first nucleic acid sequence (e.g. polynucleotide in its function as a probe for detecting a miRNA or miRNA*) will hybridize to a second nucleic acid sequence (e.g. target sequence such as nucleotide sequence of a miRNA or miRNA*), such as in a complex mixture of nucleic acids. Stringent conditions are sequence-dependent and will be different in different circumstances. Stringent conditions may be selected to be about 5 to 10°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength pH. The T_m may be the temperature (under defined ionic strength, pH, and nucleic acid concentration) at which 50% of the probes complementary to the target hybridize to the target sequence at equilibrium (as the target sequences are present in excess, at T_m , 50% of the probes are occupied at equilibrium). Stringent conditions may be those in which the salt concentration is less than about 1.0 M sodium ion, such as about 0.01 to 1.0 M sodium ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 20°C for short probes (e.g., about 10-35 nucleotides) and up to 60°C for long probes (e.g., greater than about 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide. For selective or specific hybridization, a positive signal may be at least 2 to 10 times background hybridization. Exemplary stringent hybridization conditions include the following: 50% formamide, 5x SSC, and 1% SDS, incubating at 42°C, or, 5x SSC, 1% SDS, incubating at 65°C, with wash in 0.2x SSC, and 0.1% SDS at 65°C; or 6x SSPE, 10 % formamide, 0.01 %, Tween 20, 0.1 x TE buffer, 0.5 mg/ml BSA, 0.1 mg/ml herring sperm DNA, incubating at 42°C with wash in 0.5x SSPE and 6x SSPE at 45°C.

[0029] The term "antisense", as used herein, refers to nucleotide sequences which are complementary to a specific

DNA or RNA sequence. The term "antisense strand" is used in reference to a nucleic acid strand that is complementary to the "sense" strand.

[0030] Residues in two or more polynucleotide s are said to "correspond" to each other if the residues occupy an analogous position in the polynucleotide structures. It is well known in the art that analogous positions in two or more polynucleotides can be determined by aligning the polynucleotide sequences based on nucleic acid sequence or structural similarities. Such alignment tools are well known to the person skilled in the art and can be, for example, obtained on the World Wide Web, for example, ClustalW (see www.ebi.ac.uk/clustalw) or Align (see <http://www.ebi.ac.uk/emboss/align/index.html>) using standard settings, preferably for Align EMBOSS::needle, Matrix: Blosom62, Gap Open 10.0, Gap Extend 0.5.

[0031] The term "sensitivity", as used herein, means a statistical measure of how well a binary classification test correctly identifies a condition, for example how frequently it correctly classifies a heart and cardiovascular system disease into the correct type out of two or more possible types (e.g. heart and cardiovascular system disease type and healthy type). The sensitivity for class A is the proportion of cases that are determined to belong to class "A" by the test out of the cases that are in class "A". A theoretical, optimal prediction can achieve 100% sensitivity (i.e. predict all patients from the sick group as sick).

[0032] The term "specificity", as used herein, means a statistical measure of how well a binary classification test correctly identifies a condition, for example how frequently it correctly classifies a heart and cardiovascular system disease into the correct type out of two or more possible types. The specificity for class A is the proportion of cases that are determined to belong to class "not A" by the test out of the cases that are in class "not A". A theoretical, optimal prediction can achieve 100% specificity (i.e. not predict anyone from the healthy group as sick).

[0033] The term "accuracy", as used herein, means a statistical measure for the correctness of classification or identification of sample types. The accuracy is the proportion of true results (both true positives and true negatives).

[0034] The term "acute coronary syndrome", as used herein, encompasses any group of clinical symptoms compatible with acute myocardial ischemia. Acute myocardial ischemia is chest pain due to insufficient blood supply to the heart muscle that results from coronary artery disease (also called coronary heart disease) (definition by American Heart Association). Subtypes of acute myocardial ischemia are Unstable angina (UA) and two forms of (acute) myocardial infarction (AMI or MI, heart attack), in which the heart muscle is damaged. Unstable angina (UA) (also "crescendo angina") is defined as angina pectoris that changes or worsens. The two (acute) myocardial infarction types are named according to the appearance of the electrocardiogram (ECG/EKG) as non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI).

[0035] The inventors of the present invention analysed the expression level of miRNAs in blood samples of a cohort of controls (healthy persons) and patients suffering from an acute coronary syndrome. They succeeded in determining the miRNAs that are differentially regulated in blood samples from human patients having an acute coronary syndrome compared to healthy persons (controls) (see experimental section for experimental details). Additionally, the inventors of the present invention performed hypothesis tests (e.g. t-test, limma-test) or other measure (e.g. AUC, mutual information) on the expression level of the found miRNAs, in all controls (healthy persons) and patients suffering from an acute coronary syndrome. These tests resulted in a significance value (p-value) for each miRNA. This p-value is a measure for the diagnostic power of each of these single miRNAs to discriminate between the two clinical conditions, healthy, i.e. not suffering from an acute coronary syndrome, and diseased, i.e. suffering from an acute coronary syndrome. Since a manifold of tests are carried out, one for each miRNA, the p-values may be too optimistic and, thus, over-estimate the actual discriminatory power. Hence, the p-values are corrected for multiple testing by the Benjamini Hochberg approach.

[0036] An overview of the miRNAs that are found to be significantly differentially regulated in blood samples of acute coronary syndrome and that performed best according to t-test, limma-test or AUC is provided in Figure 7 (see experimental explanations: median g1 = median intensity value of the AMI patients; median g2= median intensity value of the healthy controls; qmedian= ratio of median g1 and median g2; logqmedian= log of qmedian; ttest_rawp=p-value calculated according to ttest; ttest_adj= adjusted p-value calculated according to ttest; limma_rawp=p-value calculated according to limma-test; limma_adj=adjusted p-value calculated according to limma-test; AUC= area under the curve statistics.). Three miRNA groups are formed. The first group (group I) comprises miRNAs according to SEQ ID NO: 1 to SEQ ID NO: 153, the second group (group II) comprises miRNAs according to SEQ ID NO: 154 to 241 and the third group (group III) comprises miRNAs according to SEQ ID NO: 242 to SEQ ID NO: 283. The miRNAs comprised in the first group and second group are sorted in order of their t-test significance as described in more detail in the experimental section (see ttest_adj= adjusted p-value calculated according to ttest). In addition, the most predictive miRNAs in group I are listed first. It should be noted that the lower the ttest_adj value of a single miRNA, the higher is the diagnostic power of said miRNA.

[0037] Usually the diagnostic power of a single miRNA biomarker is not sufficient to reach high accuracy, specificity and sensitivity for discrimination between healthy persons (controls) and patients suffering from an acute coronary syndrome, hence no simple threshold method can be used for diagnostic.

[0038] However, the inventors of the present invention surprisingly found that also a single miRNA, wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, particularly of SEQ ID NO: 1 to SEQ ID NO: 153, provide high diagnostic accuracy, specificity and sensitivity in the determination of an acute coronary syndrome in human patients (see for example Figure 3, Figure 7, and Figure 29).

[0039] The inventors of the present invention also employed more than one miRNA biomarker, i.e. sets (signatures) of miRNA biomarkers, to further increase and/or improve the performance for diagnosing and/or prognosing of individuals suffering from an acute coronary syndrome.

[0040] In order to be able to discriminate between two or more clinical conditions, e.g. healthy and suffering from an acute coronary syndrome, for a defined set of miRNA biomarkers, the inventors of the present invention applied a machine learning approach (e.g. t-test, AUC, support vector machine, hierarchical clustering, or k-means) which leads to an algorithm that is trained by reference data (i.e. data of reference miRNA expression profiles from the two clinical conditions, e.g. healthy and suffering from an acute coronary syndrome, for the defined set of miRNA markers) to discriminate between the two statistical classes (i.e. two clinical conditions, e.g. healthy or suffering from an acute coronary syndrome).

[0041] The inventors of the present invention surprisingly found that this approach yields in miRNA sets (signatures) that provide high diagnostic accuracy, specificity and sensitivity in the determination of an acute coronary syndrome in human patients (see Figures 13 to 20, Figure 28, and Figure 30). Said miRNA sets (signatures) comprise at least two miRNAs, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, particularly of SEQ ID NO: 1 to SEQ ID NO: 153. The inventors of the present invention further found that the sets of at least two miRNAs, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, can be completed by at least one further miRNA, wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, preferably in order to improve the diagnostic accuracy, specificity and sensitivity in the determination of an acute coronary syndrome.

[0042] An exemplarily approach to arrive at miRNA sets/signatures that correlate with an acute coronary syndrome is summarized below. In addition, the general work flow is shown in Figure 21.

Step 1: Total RNA (or subfractions thereof) is extracted from blood (including plasma, serum, PBMC or other blood fractions) using suitable kits and/or purification methods.

Step 2: From the respective samples, the quantity (expression level) of one miRNA or sets of at least two miRNAs selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, particularly of SEQ ID NO: 1 to SEQ ID NO: 153, is measured using experimental techniques. These techniques include but are not restricted to: array based approaches, amplification methods (PCR, RT-PCR, qPCR), sequencing, next generation sequencing, and mass spectroscopy.

Step 3: In order to gather information on the diagnostic/prognostic value and the redundancy of each of the single miRNA biomarkers, mathematical methods are applied. These methods include, but are not restricted to basic mathematic approaches (e.g. Fold Quotients, Signal to Noise ratios, Correlation), statistical methods as hypothesis tests (e.g. t-test, Wilcoxon-Mann-Whitney test), the Area under the Receiver operator Characteristics Curve, information theory approaches, (e.g. the Mutual Information, Cross-entropy), probability theory (e.g. joint and conditional probabilities) or combinations and modifications of the previously mentioned methods.

Step 4: The information gathered in step 3) is used to estimate for each miRNA biomarker the diagnostic content or value. Usually, however, this diagnostic value is too small to get a highly accurate diagnosis with accuracy rates, specificities and sensitivities beyond the 80%, particularly 90% barrier.

The diagnostic content of the miRNAs suitable for diagnosing/prognosing an acute coronary syndrome is listed in Figure 7. This table includes said miRNAs (SEQ ID NO: 1 to SEQ ID NO: 283, particularly SEQ ID NO: 1 to SEQ ID NO: 153) (Experimental explanations: median g1 = median intensity value of the AMI patients; median g2= median intensity value of the healthy controls; qmedian= ratio of median g1 and median g2; logqmedian= log of qmedian; and the statistical significance value as computed by a t-test, limma-test or AUC-test : ttest_rawp=p-value calculated according to ttest; ttest_adj= adjusted p-value calculated according to ttest; limma_rawp=p-value calculated according to limma-test; limma_adj=adjusted p-value calculated according to limma-test; AUC= area under the curve).

Step 5: In order to use increase the performance for diagnosing/prognosing of individuals suffering from an acute coronary syndrome, more than one miRNA biomarker need to be employed. Thus statistical learning / machine learning / bioinformatics / computational approaches are applied for set selection in order to select/define sets of miRNA biomarkers (comprising miRNAs SEQ ID NO: 1 to SEQ ID NO: 283, particularly SEQ ID NO: 1 to SEQ ID NO: 153) that are tailored for the detection of an acute coronary syndrome. These techniques include but are not restricted to: Wrapper subset selection techniques (e.g. forward step-wise, backward step-wise, combinatorial approaches, optimization approaches), filter subset selection methods (e.g. the methods

mentioned in Step 3), principal component analysis, or combinations and modifications of such methods (e.g. hybrid approaches).

Step 6: The subsets, selected/defined in Step 5, which may range from only a small number (at least two for the set) to all measured biomarkers is then used to carry out a diagnosis/prognosis of an acute coronary syndrome. To this end, statistical learning / machine learning / bioinformatics / computational approaches are applied that include but are not restricted to any type of supervised or unsupervised analysis: classification techniques (e.g. naive Bayes, Linear Discriminant Analysis, Quadratic Discriminant Analysis Neural Nets, Tree based approaches, Support Vector Machines, Nearest Neighbour Approaches), Regression techniques (e.g. linear Regression, Multiple Regression, logistic regression, probit regression, ordinal logistic regression ordinal Probit-Regression, Poisson Regression, negative binomial Regression, multinomial logistic Regression, truncated regression), Clustering techniques (e.g. k-means clustering, hierarchical clustering, PCA), Adaptations, extensions, and combinations of the previously mentioned approaches.

[0043] By combination of subset selection (Step 5) and machine learning (Step 6) an algorithm or mathematical function for diagnosing/prognosing an acute coronary syndrome is obtained. This algorithm or mathematical function is applied to a miRNA expression profile of an individual to be diagnosed for an acute coronary syndrome.

[0044] Thus, in a first aspect, the present invention relates to (the use of) a (single) polynucleotide for detecting a (single) miRNA or a set (signature) comprising, essentially consisting of, or consisting of at least two polynucleotides for detecting a set (signature) comprising, essentially consisting of, or consisting of at least two miRNAs for diagnosing and/or prognosing of an acute coronary syndrome, preferably myocardial infarction or Unstable angina (UA), in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283.

[0045] In preferred embodiments, the blood sample from a human is whole blood or a blood fraction such as serum or plasma. It is also preferred to use blood cells also known as hemopoietic cells. The term "hemopoietic cells" refers to mature cell types and their immature precursors that are identifiable either by morphology or, mostly, by a distinct pattern of cell surface markers. The term is used to distinguish these cells from other cell types found in the body and also includes T-cells and distinctive subsets, which are the only hematopoietic cells that are not generated in the bone marrow. Preferably, the blood cells are erythrocytes, leukocytes and/or thrombocytes. It is also preferred to use peripheral blood mononuclear cells (PBMCs) such as lymphocytes, monocytes or macrophages.

[0046] Preferably, the blood sample from a human has a volume of between 0.1 and 20 ml, more preferably of between 0.5 and 10 ml, i.e. 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 ml. It is preferred that the blood sample is from a human that has not been therapeutically treated or has been therapeutically treated. In one embodiment, the therapeutical treatment is monitored on the basis of the detection of the miRNA or set of miRNAs by the nucleotide or set of polynucleotides. It is also preferred that total RNA or subfractions thereof, isolated (e.g. extracted) from a blood sample of a human is used for detecting the miRNA or set of miRNAs by the polynucleotide or set of polynucleotides.

[0047] The polynucleotide or polynucleotides comprised in the set of the present invention may be single stranded or double stranded. The skilled person in the art will understand that the polynucleotide as a single polynucleotide strand provides a probe (e.g. miRNA capture probe) that is capable of binding to, hybridizing with, or detecting a target miRNA of complementary sequence through one or more types of chemical bonds, usually through complementary base pairing, usually through hydrogen bond formation.

[0048] It is preferred that the polynucleotides of the present invention are for detecting a set comprising, essentially consisting of, or consisting of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282 miRNAs, or comprising/consisting of 283 miRNAs, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283.

[0049] It is particularly preferred that the number of polynucleotides is equivalent to the number of miRNAs comprised in the set.

[0050] It is more preferred that the present invention relates to (the use of) a (single) polynucleotide for detecting a

(single) miRNA or a set (signature) comprising, essentially consisting of, or consisting of at least two polynucleotides for detecting a set (signature) comprising, essentially consisting of, or consisting of at least two miRNAs for diagnosing and/or prognosing of an acute coronary syndrome, preferably myocardial infarction or Unstable angina (UA), in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153.

[0051] It is particularly more preferred that the polynucleotides of the present invention are for detecting a set comprising, essentially consisting of, or consisting of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 miRNAs, or comprising/consisting of 153 miRNAs, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153.

[0052] Preferably, the nucleotide sequences of the at least 2 miRNAs comprised in the set have SEQ ID NO: 1 and SEQ ID NO: 2, the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 3, the nucleotide sequences of the at least 4 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 4, the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 5, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 6, the nucleotide sequences of the at least 7 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 7, the nucleotide sequences of the at least 8 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 8, the nucleotide sequences of the at least 9 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 9, the nucleotide sequences of the at least 10 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 10, the nucleotide sequences of the at least 11 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 11, the nucleotide sequences of the at least 12 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 12, the nucleotide sequences of the at least 13 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 13, the nucleotide sequences of the at least 14 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 14, the nucleotide sequences of the at least 15 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 15, the nucleotide sequences of the at least 16 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 16, the nucleotide sequences of the at least 17 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 17, the nucleotide sequences of the at least 18 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 18, the nucleotide sequences of the at least 19 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 19, the nucleotide sequences of the at least 20 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 20, the nucleotide sequences of the at least 21 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 21, the nucleotide sequences of the at least 22 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 22, the nucleotide sequences of the at least 23 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 23, the nucleotide sequences of the at least 24 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 24, the nucleotide sequences of the at least 25 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 25, the nucleotide sequences of the at least 26 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 26, the nucleotide sequences of the at least 27 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 27, the nucleotide sequences of the at least 28 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 28, the nucleotide sequences of the at least 29 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 29, the nucleotide sequences of the at least 30 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 30, the nucleotide sequences of the at least 31 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 31, the nucleotide sequences of the at least 32 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 32, the nucleotide sequences of the at least 33 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 33, the nucleotide sequences of the at least 34 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 34, the nucleotide sequences of the at least 35 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 35, the nucleotide sequences of the at least 36 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 36, the nucleotide sequences of the at least 37 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 37, the nucleotide sequences of the at least 38 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 38, the nucleotide sequences of the at least 39 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 39, the nucleotide sequences of the at least 40 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 40, the nucleotide sequences of the at least 41 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 41, the nucleotide sequences of the at least 42 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 42, the nucleotide sequences of the at least 43 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 43, the nucleotide sequences of the at least 44 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 44, the nucleotide sequences of the at least 45 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 45, the nucleotide sequences of the at least 46 miRNAs

[illegible]

[illegible]

[0053] It is also preferred that the nucleotide sequences of the at least 2 miRNAs comprised in the set have SEQ ID NO: 1 and SEQ ID NO: 2, the nucleotide sequences of the at least 2 miRNAs comprised in the set have SEQ ID NO: 3 and SEQ ID NO: 4, the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7, the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10, the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 11, SEQ ID NO: 12, and SEQ ID NO: 13, the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 14, SEQ ID NO: 15, and SEQ ID NO: 16, the nucleotide sequences of the at least 4 miRNAs comprised in the set have SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, and SEQ ID NO: 20, the nucleotide sequences

of the at least 4 miRNAs comprised in the set have SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, and SEQ ID NO: 24, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, and SEQ ID NO: 48, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, and SEQ ID NO: 54, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, and SEQ ID NO: 60, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 66, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, and SEQ ID NO: 72, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, and SEQ ID NO: 78, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, and SEQ ID NO: 84, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 90, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, and SEQ ID NO: 102, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, and SEQ ID NO: 108, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, and SEQ ID NO: 114, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, and SEQ ID NO: 120, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, and SEQ ID NO: 126, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, and SEQ ID NO: 132, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 138, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, and SEQ ID NO: 144, the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, and SEQ ID NO: 149, or the nucleotide sequences of the at least 4 miRNAs comprised in the set have SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, and SEQ ID NO: 153.

[0054] It is particularly preferred that the nucleotide sequences of the at least 10 miRNAs comprised in the set have SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a), or have SEQ ID NO: 1 to SEQ ID NO: 10.

[0055] It is also particularly preferred that

- (i) the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 3 and SEQ ID NO: 2,
- (ii) the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 1, SEQ ID NO: 5, SEQ ID NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22,
- (iii) the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 2, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18 and SEQ ID NO: 24,
- (iv) the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 1, SEQ ID NO: 34, SEQ ID NO: 30, SEQ ID NO: 22 and SEQ ID NO: 28,
- (v) that the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 2, SEQ ID NO: 17, SEQ ID NO: 81, SEQ ID NO: 1 and SEQ ID NO: 34,
- (vi) that the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 45, SEQ ID NO: 7, SEQ ID NO: 6, SEQ ID NO: 37 and SEQ ID NO: 90, or
- (vii) the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 1, SEQ ID NO: 5, SEQ ID NO: 19, SEQ ID NO: 20 and SEQ ID NO: 21.

[0056] The above-mentioned sets may also be combined with each other, e.g. (i) with (ii), (ii) with (iii), (iii) with (iv), (iv) with (v), (v) with (vi), (vi) with (vii), etc..

[0057] Preferably, the polynucleotides of the present invention are for detecting a set (signature) as defined above comprising at least one further miRNA, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 further miRNA(s), wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241.

[0058] Accordingly, it is preferred that the polynucleotides of the present invention are for detecting a set (signature) comprising, essentially consisting of, or consisting of at least two miRNAs for diagnosing and/or prognosing of an acute coronary syndrome, preferably myocardial infarction or Unstable angina (UA), in a blood sample from a human, particularly human patient, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, and wherein the polynucleotides of the present invention are for detecting a set (signature) comprising at least one further miRNA, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 further miRNA(s), wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241.

[0059] Thus, in a preferred embodiment of the present invention, the polynucleotides of the present invention are for detecting a set comprising at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153 miRNAs, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, and the polynucleotides of the present invention are for detecting

- (i) at least one further miRNA having the nucleotide sequence according to SEQ ID NO: 154,
- (ii) at least 2 further miRNAs having the nucleotide sequence according to SEQ ID NO: 154 and SEQ ID NO: 155,
- (iii) at least 3 further miRNAs having the nucleotide sequence according to SEQ ID NO: 154 to SEQ ID NO: 156,
- (iv) at least 4 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 157,
- (v) at least 5 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 158,
- (vi) at least 6 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 159, or
- (vii) at least 7 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 160,

which is (are) also comprised in said set of miRNAs.

[0060] In another preferred embodiment of the present invention, the polynucleotides of the present invention are for detecting a set comprising at least 10 miRNAs, wherein the nucleotide sequences of the at least 10 miRNAs comprised in the set have SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a), or have SEQ ID NO: 1 to SEQ ID NO: 10, and the polynucleotides of the present invention are for detecting

- (i) at least one further miRNA having the nucleotide sequence according to SEQ ID NO: 154,
- (ii) at least 2 further miRNAs having the nucleotide sequence according to SEQ ID NO: 154 and SEQ ID NO: 155,
- (iii) at least 3 further miRNAs having the nucleotide sequence according to SEQ ID NO: 154 to SEQ ID NO: 156,
- (iv) at least 4 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 157,
- (v) at least 5 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 158,
- (vi) at least 6 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 159, or
- (vii) at least 7 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 160,

which is (are) also comprised in said set of miRNAs.

[0061] It is also preferred that the polynucleotide(s) of the present invention is (are) for detecting a miRNA or a set comprising, essentially consisting of, or consisting of at least two miRNAs for diagnosing and/or prognosing of an acute coronary syndrome, preferably myocardial infarction or Unstable angina (UA), in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from SEQ ID NO: 242 to SEQ ID NO: 283.

[0062] It is further preferred that the polynucleotides of the present invention are for detecting a set (signature) comprising, essentially consisting of, or consisting of at least two miRNAs for diagnosing and/or prognosing of an acute coronary syndrome, preferably myocardial infarction or Unstable angina (UA), in a blood sample from a human, particularly human patient, wherein the nucleotide sequences of said miRNAs are selected from one or more sets listed in Figure 28 and/or Figure 30. For example, the nucleotide sequences of said miRNAs may be selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more sets listed in Figure 28 and/or Figure 30. Thus, polynucleotides or individual sets of polynucleotides for detecting sets comprising at least two miRNAs may also be combined with each other, e.g. polynucleotides for detecting Set No. 1 with polynucleotides for detecting Set No. 2, polynucleotides for detecting Set No. 2 with polynucleotides for detecting Set No. 3, polynucleotides for detecting Set No. 1 with polynucleotides for detecting Set No. 2 and Set No. 3, polynucleotides for detecting Set No. 3 with polynucleotides for detecting Set No. 5 and Set No. 8, etc.

[0063] Furthermore, it is preferred that

- (i) the polynucleotide of the present invention is complementary to the miRNA, wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, or the polynucleotides comprised in the set of the present invention are complementary to the miRNAs comprised in the set, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283,
- (ii) the polynucleotide is a fragment of the polynucleotide according to (i), preferably the polynucleotide is a fragment which is between 1 and 12, more preferably between 1 and 8, and most preferably between 1 and 5 or 1 and 3, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, nucleotides shorter than the polynucleotide according to (i), or the polynucleotides comprised in the set are fragments of the polynucleotides comprised in the set according to (i), preferably the polynucleotides comprised in the set are fragments which are between 1 and 12, more preferably between 1 and 8, and most preferably between 1 and 5 or 1 and 3, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, nucleotides shorter than the polynucleotides comprised in the set according to (i), or
- (iii) the polynucleotide has at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% or 99%, i.e. 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%, sequence identity to the polynucleotide sequence of the polynucleotide according to (i) or polynucleotide fragment according to (ii), or the polynucleotides comprised in the set have at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% or 99%, i.e. 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%, sequence identity to the polynucleotide sequences of the polynucleotides comprised in the set according to (i) or polynucleotide fragments comprised in the set according to (ii), and

[0064] It is more preferred that

- (i) the polynucleotide of the present invention is complementary to the miRNA, wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, or the polynucleotides comprised in the set of the present invention are complementary to the miRNAs comprised in the set, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, and preferably, wherein the nucleotide sequence of the at least one further miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241,
- (ii) the polynucleotide is a fragment of the polynucleotide according to (i), preferably the polynucleotide is a fragment which is between 1 and 12, more preferably between 1 and 8, and most preferably between 1 and 5 or 1 and 3, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, nucleotides shorter than the polynucleotide according to (i), or the polynucleotides comprised in the set are fragments of the polynucleotides comprised in the set according to (i), preferably the polynucleotides comprised in the set are fragments which are between 1 and 12, more preferably between 1 and 8, and most preferably between 1 and 5 or 1 and 3, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, nucleotides shorter than the polynucleotides comprised in the set according to (i), or
- (iii) the polynucleotide has at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% or 99%, i.e. 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%, sequence identity to the polynucleotide sequence of the polynucleotide according to (i) or polynucleotide fragment according to (ii), or the polynucleotides comprised in the set have at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% or 99%, i.e. 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%, sequence identity to the polynucleotide sequences of the polynucleotides comprised in the set according to (i) or polynucleotide fragments comprised in the set according to (ii).

[0065] It is particularly preferred that the polynucleotide as defined in (iii) has at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% or 99%, i.e. 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90,

91, 92, 93, 94, 95, 96, 97, 98, or 99%, sequence identity over a continuous stretch of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more nucleotides, preferably over the whole length, to the polynucleotide sequence of the polynucleotide according to (i) or polynucleotide fragment according to (ii), or that the polynucleotides comprised in the set as defined in (iii) have at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% or 99%, i.e. 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%, sequence identity over a continuous stretch of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more nucleotides, preferably over the whole length, to the polynucleotide sequences of the polynucleotides comprised in the set according to (i) or polynucleotide fragments comprised in the set according to (ii).

[0066] In addition, the polynucleotide or polynucleotides as defined in (ii) (i.e. polynucleotide fragment(s)) or (iii) (i.e. polynucleotide variant(s) or polynucleotide fragment variant(s)) is (are) only regarded as a polynucleotide or polynucleotides as defined in (ii) (i.e. polynucleotide fragment(s)) or (iii) (i.e. polynucleotide variant(s) or polynucleotide fragment variant(s)) within the context of the present invention, if it is or they are still capable of binding to, hybridizing with, or detecting a target miRNA of complementary sequence or target miRNAs of complementary sequences, e.g. the respective target miRNA(s) according to SEQ ID NO: 1 to SEQ ID NO: 283, or particularly according to SEQ ID NO: 1 to SEQ ID NO: 241, through one or more types of chemical bonds, usually through complementary base pairing, usually through hydrogen bond formation under stringent hybridization conditions. The skilled person can readily assess whether a polynucleotide or polynucleotides as defined in (ii) (i.e. polynucleotide fragment(s)) or (iii) (i.e. polynucleotide variant(s) or polynucleotide fragment variant(s)) is (are) still capable of binding to, hybridizing with, recognizing or detecting a target miRNA of complementary sequence or target miRNAs of complementary sequences, e.g. the respective target miRNA(s) according to SEQ ID NO: 1 to SEQ ID NO: 283, or particularly according to SEQ ID NO: 1 to SEQ ID NO: 241. Suitable assays to determine whether hybridization under stringent conditions still occurs are well known in the art. However, as an example, a suitable assay to determine whether hybridization still occurs comprises the steps of: (a) incubating the polynucleotide or polynucleotides as defined in (ii) or (iii) attached onto a biochip with the miRNA(s) of complementary sequence(s), e.g. the respective target miRNA(s) according to SEQ ID NO: 1 to SEQ ID NO: 283, or particularly according to SEQ ID NO: 1 to SEQ ID NO: 241, labeled with biotin under stringent hybridization conditions, (b) washing the biochip to remove unspecific bindings, (c) subjecting the biochip to a detection system, and (c) analyzing whether the polynucleotide(s) can still hybridize with the target miRNA(s) of complementary sequence(s), e.g. the respective target miRNA(s) according to SEQ ID NO: 1 to SEQ ID NO: 283, or particularly according to SEQ ID NO: 1 to SEQ ID NO: 241. As a positive control, the respective non-mutated and not fragmented polynucleotide as defined in (i) may be used. Preferably stringent hybridization conditions include the following: 50% formamide, 5x SSC, and 1% SDS, incubating at 42°C, or, 5x SSC, 1% SDS, incubating at 65°C, with wash in 0.2x SSC, and 0.1% SDS at 65°C; or 6x SSPE, 10 % formamide, 0.01 %, Tween 20, 0.1 x TE buffer, 0.5 mg/ml BSA, 0.1 mg/ml herring sperm DNA, incubating at 42°C with wash in 0.5x SSPE and 6x SSPE at 45°C.

[0067] In a preferred embodiment, the polynucleotide of the present invention is for detecting a nucleotide sequence of a miRNA selected from the group consisting of SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a), or selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 10. It is particularly preferred that the polynucleotide is for detecting the nucleotide sequence of the miRNA of SEQ ID NO: 1 (hsa-miR-1291).

[0068] In another preferred embodiment, the polynucleotide of the present invention is for detecting a nucleotide sequence of a miRNA listed in Figure 29.

[0069] In a second aspect, the present invention provides a method for diagnosing and/or prognosing of an acute coronary syndrome comprising the steps of:

- (i) determining an expression profile of a miRNA or a set (signature) comprising, essentially consisting of, or consisting of at least two miRNAs representative for an acute coronary syndrome, preferably myocardial infarction or Unstable angina (UA), in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, a fragment thereof, and a sequence having at least 80% sequence identity thereto, and
- (ii) comparing said expression profile to a reference, wherein the comparison of said expression profile to said reference allows for the diagnosis and/or prognosis of an acute coronary syndrome and/or applying an algorithm or a mathematical function to said expression profile, wherein the application of said algorithm or mathematical function to said expression profile allows for the diagnosis and/or prognosis of an acute coronary syndrome.

[0070] Preferably, the method for diagnosing and/or prognosing of an acute coronary syndrome comprises the steps of:

- (i) determining an expression profile of a miRNA or a set (signature) comprising, essentially consisting of, or consisting of at least two miRNAs representative for an acute coronary syndrome, preferably myocardial infarction or Unstable

angina (UA), in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, a fragment thereof, and a sequence having at least 80% sequence identity thereto, and
 (ii) comparing said expression profile to a reference, wherein the comparison of said expression profile to said
 5 reference allows for the diagnosis and/or prognosis of an acute coronary syndrome and/or applying an algorithm or a mathematical function to said expression profile, wherein the application of said algorithm or mathematical function to said expression profile allows for the diagnosis and/or prognosis of an acute coronary syndrome.

[0071] The term "miRNA expression profile", as used herein, represents the expression level of a single miRNA or a
 10 collection of expression levels of at least two miRNAs comprised in a set (signature), preferably of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127,
 15 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247,
 20 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, or 283 miRNAs, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283.

[0072] In a preferred embodiment, the term "miRNA expression profile", as used herein, represents the expression
 25 level of a single miRNA or a collection of expression levels of at least two miRNAs comprised in a set (signature), preferably of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121,
 30 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, or 153 miRNAs, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, and more preferably of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64,
 35 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192,
 40 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, or 241 miRNAs, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 241.

[0073] According to the method of the present invention, the expression profile of a single miRNA or the expression
 45 profile of miRNAs comprised in a set is determined in a blood sample from a human. This is possible, as the miRNAs disclosed herein are expressed within and/or among cells or tissues and are subsequently released/transferred into circulating blood and/or as the miRNAs described herein are directly expressed in hemopoietic cells, also known as blood cells, e.g. erythrocytes, leukocytes and/or thrombocytes. Thus, the terms generating "an expression profile of miRNAs in a blood sample" by determining "miRNA expression levels in a blood sample" do not solely mean that said
 50 miRNAs are actually expressed in blood. Said terms refer to both miRNAs which are expressed in surrounding cells or tissues and are subsequently released into circulating blood and miRNAs which are directly expressed in blood, namely in blood cells, e.g. peripheral blood mononuclear cells (PBMCs). Accordingly, the expression levels of miRNAs determined in a blood sample indirectly represent the expression levels of that miRNAs in the cells or tissues from which they originate and/or directly represent the expression levels of miRNAs in blood cells.

[0074] Said miRNA expression profiles may be generated by any convenient means for determining a miRNA level, e.g. hybridization of miRNA, labeled miRNA, or amplified miRNA (e.g. to a microarray), quantitative PCR (qPCR) such as real time quantitative PCR (RT qPCR), ELISA for quantitation, next generation sequencing and the like and allow the analysis of differential miRNA expression levels between two blood samples, e.g. whole blood, serum, or plasma samples.

Thus, for example, the differential miRNA level may be determined between a whole blood sample of a person having an acute coronary syndrome and a whole blood sample of a healthy person. The blood sample, e.g. whole blood, serum, or plasma sample, may be collected by any convenient method, as known in the art. Thereby, each miRNA is represented by a numerical value. The higher the value of an individual miRNA, the higher is the expression level of said miRNA.

5 The miRNA expression profile may include expression data for 1, 2, 3, 4, 5, 7, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 75, 100, or 153 miRNAs, preferably for 241 miRNAs, including miRNAs selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153 disclosed herein, preferably further including miRNAs selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241 disclosed herein.

10 **[0075]** The term "differential expression" of miRNA as used herein, means qualitative and/or quantitative differences in the temporal and/or cellular miRNA expression patterns within and/or among cells, tissues, or within blood. Thus, a differentially expressed miRNA may qualitatively have its expression altered, including an activation or inactivation in, for example, normal tissue versus disease tissue. The difference in miRNA expression may also be quantitative, e.g. in that expression is modulated, i.e. either up-regulated, resulting in an increased amount of miRNA, or down-regulated, resulting in a decreased amount of miRNA. The degree to which miRNA expression differs need only be large enough

15 to be quantified via standard characterization techniques, e.g. quantitative hybridization of miRNA, labeled miRNA, or amplified miRNA, quantitative PCR (qPCR) such as real time quantitative PCR (RT qPCR), ELISA for quantitation, next generation sequencing and the like. As mentioned above, the expression profile of a single miRNA or the expression profile of miRNAs comprised in a set described herein is obtained from a blood sample, e.g. whole blood, blood serum, or blood plasma. This does not necessarily require that the miRNA is differentially expressed in blood. It can be differentially expressed in blood cells but it can also be expressed in surrounding cells or tissues and can be subsequently released/transferred into circulating blood or can be end up in blood by other mechanisms. Therefore, the differentially expression level of a miRNA determined in a blood sample represents a measure for diagnosing a clinical condition, e.g. an acute coronary syndrome.

25 **[0076]** The term "a single miRNA or a set comprising at least two miRNAs representative for an acute coronary syndrome", as used herein, refers to a fixed defined single miRNA which is known to be differential between human patients having an acute coronary syndrome (diseased state) and healthy humans (normal/control state) and, thus, representative for an acute coronary syndrome, or to at least two miRNAs comprised in a set which are known to be differential between human patients having an acute coronary syndrome (diseased state) and healthy humans (normal/control state) and, thus, representative for an acute coronary syndrome. The nucleotide sequence of said fixed

30 defined single miRNA or the nucleotide sequences of said at least two fixed defined miRNAs comprised in the set is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283. In a preferred embodiment, the nucleotide sequence of said fixed defined single miRNA or the nucleotide sequences of said at least two fixed defined miRNAs comprised in the set is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153. The above-mentioned set may be supplemented by at least one further miRNA, wherein the nucleotide sequence of said miRNA is selected from group consisting of SEQ ID NO: 154 to SEQ ID NO: 241.

35 **[0077]** As already mentioned above, the inventors of the present invention analysed the expression level of miRNAs in blood samples of a cohort of controls (healthy persons) and patients suffering from an acute coronary syndrome. They succeeded in determining the miRNAs that are differentially regulated in blood samples from human patients having an acute coronary syndrome compared to healthy persons (controls) (see experimental section for details).

40 **[0078]** An overview of the 283 miRNAs (SEQ ID NO: 1 to SEQ ID NO: 283, particularly SEQ ID NO: 1 to SEQ ID NO: 241) that are found to be significantly differentially regulated in blood samples of acute coronary syndrome is provided in Figure 7. Three groups are formed. The first group (group I) comprises miRNAs according to SEQ ID NO: 1 to SEQ ID NO: 153, the second group (group II) comprises miRNAs according to SEQ ID NO: 154 to SEQ ID NO: 241, and the third group (group III) comprises miRNAs according to SEQ ID NO: 242 to SEQ ID NO: 283. The miRNAs comprised in

45 the first group and second group are sorted in order of their t-test significance as described in more detail in the experimental section (see $ttest_adjp$ = adjusted p-value calculated according to ttest). The most predictive miRNAs in group I are listed first. It should be noted that the lower the $ttest_adjp$ value of a single miRNA, the higher is the diagnostic power of said miRNA.

50 **[0079]** Thus, for analysis of a human blood sample in step (i) of the method of the present invention, an expression profile of a fixed defined single miRNA which is known to be differential between human patients having an acute coronary syndrome (diseased state) and healthy humans (normal/control state) and, thus, representative for an acute coronary syndrome, or a set comprising at least two miRNAs which are known to be differential between human patients having an acute coronary syndrome (diseased state) and healthy humans (normal/control state) and, thus, representative for an acute coronary syndrome, is determined, wherein the nucleotide sequence of said miRNA or the nucleotide sequences

55 of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283. In preferred embodiments, the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153. In addition, for further analysis of said human blood sample in step (i) of the method of the present invention, at least one further miRNA which is known to be differential between human

patients having an acute coronary syndrome (diseased state) and healthy humans (normal/control state) and, thus, also representative for an acute coronary syndrome, wherein the nucleotide sequence is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, may be added to the fixed defined set of at least two miRNAs, wherein the nucleotide sequences are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, and an expression profile may be determined from this supplemented set, for example, to improve the diagnostic accuracy, specificity and sensitivity in the determination of an acute coronary syndrome.

[0080] The inventors of the present invention have found that single miRNAs or sets of at least two miRNAs, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, particularly of SEQ ID NO: 1 to SEQ ID NO: 153, provide high diagnostic accuracy, specificity and sensitivity in the determination of an acute coronary syndrome in human patients (see for example Figure 3, Figure 7, and Figure 29 (t-test, limma-test, and AUC values) for single miRNAs and Figures 13 to 20, Figure 28, and Figure 30 for miRNA sets/signatures). The inventors of the present invention further found that the sets of at least two miRNAs, wherein the nucleotide sequence of said miRNA or nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, can be completed by at least one further miRNA, wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, preferably in order to improve the diagnostic accuracy, specificity and sensitivity in the determination of an acute coronary syndrome.

[0081] For human blood analysis, it may be required that a polynucleotide (probe) capable of detecting this fixed defined miRNA or polynucleotides (probes) capable of detecting these fixed defined miRNA set is (are) attached to a solid support, substrate, surface, platform, or matrix, e.g. biochip, which may be used for blood sample analysis. For example, if the fixed defined set of miRNAs for diagnosing an acute coronary syndrome may comprises or consists of 30 miRNAs, polynucleotides capable of detecting these 30 miRNAs may be attached to a solid support, substrate, surface, platform or matrix, e.g. biochip, in order to perform the diagnostic sample analysis.

[0082] As mentioned above, an expression profile of a miRNA or a set comprising, essentially consisting of, or consisting of at least two miRNAs representative for an acute coronary syndrome in a blood sample is determined in step (i) of the method of the present invention, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283. In preferred embodiments of the method of the present invention, the set comprises, essentially consists of, or consists of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282 miRNAs, or comprises/consists of 283 miRNAs, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283.

[0083] In more preferred embodiments of the method of the present invention, an expression profile of a miRNA or a set comprising, essentially consisting of, or consisting of at least two miRNAs representative for an acute coronary syndrome in a blood sample is determined in step (i) of the method of the present invention, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153. In particularly more preferred embodiments of the method of the present invention, the set comprises, essentially consists of, or consists of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, or 152 miRNAs, or comprises/consists of 153 miRNAs, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153.

[0084] Preferably, the nucleotide sequences of the at least 2 miRNAs comprised in the set have SEQ ID NO: 1 and SEQ ID NO: 2, the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 3, the nucleotide sequences of the at least 4 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 4, the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 5, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 6, the nucleotide

[illegible]

[illegible]

[illegible]

[0085] It is also preferred that the nucleotide sequences of the at least 2 miRNAs comprised in the set have SEQ ID NO: 1 and SEQ ID NO: 2, the nucleotide sequences of the at least 2 miRNAs comprised in the set have SEQ ID NO: 3 and SEQ ID NO: 4, the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7, the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10, the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 11, SEQ ID NO: 12, and SEQ ID NO: 13, the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 14, SEQ ID NO: 15, and SEQ ID NO: 16, the nucleotide sequences of the at least 4 miRNAs comprised in the set have SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, and SEQ ID NO: 20, the nucleotide sequences of the at least 4 miRNAs comprised in the set have SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, and SEQ ID NO: 24, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, and SEQ ID NO: 48, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, and SEQ ID NO: 54, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, and SEQ ID NO: 60, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 66, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, and SEQ ID NO: 72, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, and SEQ ID NO: 78, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, and SEQ ID NO: 84, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 90, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, and SEQ ID NO: 100.

93, SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, and SEQ ID NO: 102, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, and SEQ ID NO: 108, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, and SEQ ID NO: 114, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, and SEQ ID NO: 120, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, and SEQ ID NO: 126, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, and SEQ ID NO: 132, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 138, the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, and SEQ ID NO: 144, the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, and SEQ ID NO: 149, or the nucleotide sequences of the at least 4 miRNAs comprised in the set have SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, and SEQ ID NO: 153.

[0086] In a preferred embodiment of the method of the present invention, an expression profile of a set comprising at least 10 miRNAs is determined in step (i), wherein the nucleotide sequences of the at least 10 miRNAs comprised in the set have SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a), or have SEQ ID NO: 1 to SEQ ID NO: 10.

[0087] It is also particularly preferred that

- (i) the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 3 and SEQ ID NO: 2,
- (ii) the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 1, SEQ ID NO: 5, SEQ ID NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22,
- (iii) the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 2, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18 and SEQ ID NO: 24,
- (iv) the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 1, SEQ ID NO: 34, SEQ ID NO: 30, SEQ ID NO: 22 and SEQ ID NO: 28,
- (v) that the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 2, SEQ ID NO: 17, SEQ ID NO: 81, SEQ ID NO: 1 and SEQ ID NO: 34,
- (vi) that the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 45, SEQ ID NO: 7, SEQ ID NO: 6, SEQ ID NO: 37 and SEQ ID NO: 90, or
- (vii) the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 1, SEQ ID NO: 5, SEQ ID NO: 19, SEQ ID NO: 20 and SEQ ID NO: 21.

[0088] The above-mentioned sets may also be combined with each other, e.g. (i) with (ii), (ii) with (iii), (iii) with (iv), (iv) with (v), (v) with (vi), (vi) with (vii), etc..

[0089] Preferably, the set (signature) as defined above comprises at least one further miRNA, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 further miRNA(s), wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, a fragment thereof, and a sequence having at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% or 99%, i.e. 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%, sequence identity thereto. Accordingly, it is preferred that the set (signature) comprising, essentially consisting of, or consisting of at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, comprises at least one further miRNA, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 further miRNA(s), wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, a fragment thereof, and a sequence having at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% or 99%, i.e. 80,

81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%, sequence identity thereto.

[0090] Thus, in a preferred embodiment of the method of the present invention, the set comprising at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153 miRNAs, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, and comprises

- (i) at least one further miRNA having the nucleotide sequence according to SEQ ID NO: 154,
- (ii) at least 2 further miRNAs having the nucleotide sequence according to SEQ ID NO: 154 and SEQ ID NO: 155,
- (iii) at least 3 further miRNAs having the nucleotide sequence according to SEQ ID NO: 154 to SEQ ID NO: 156,
- (iv) at least 4 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 157,
- (v) at least 5 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 158,
- (vi) at least 6 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 159, or
- (vii) at least 7 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 160.

[0091] In another preferred embodiment of the method of the present invention, the set in step (i) comprises at least 10 miRNAs, wherein the nucleotide sequences of the at least 10 miRNAs comprised in the set have SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a), or have SEQ ID NO: 1 to SEQ ID NO: 10, and comprises

- (i) at least one further miRNA having the nucleotide sequence according to SEQ ID NO: 154,
- (ii) at least 2 further miRNAs having the nucleotide sequence according to SEQ ID NO: 154 and SEQ ID NO: 155,
- (iii) at least 3 further miRNAs having the nucleotide sequence according to SEQ ID NO: 154 to SEQ ID NO: 156,
- (iv) at least 4 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 157,
- (v) at least 5 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 158,
- (vi) at least 6 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 159, or
- (vii) at least 7 further miRNAs having the nucleotide sequences according to SEQ ID NO: 154 to SEQ ID NO: 160.

[0092] It is also preferred that an expression profile of a miRNA or a set (signature) comprising, essentially consisting of, or consisting of at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, is determined in the first step of the method of the present invention, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from SEQ ID NO: 242 to SEQ ID NO: 283.

[0093] It is further preferred that an expression profile of a set (signature) comprising, essentially consisting of, or consisting of at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, is determined in the first step of the method of the present invention, wherein the nucleotide sequences of said miRNAs are selected from one or more sets listed in Figure 28 and/or Figure 30. For example, the nucleotide sequences of said miRNAs may be selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more sets listed in Figure 28 and/or Figure 30. Thus, the individual miRNA sets may also be combined with each other, e.g. miRNAs of Set No. 1 with miRNAs of Set No. 2, miRNAs of Set No. 2 with miRNAs of Set No. 3, miRNAs of Set No. 1 with miRNAs of Set No. 2 and Set No. 3, miRNAs of Set No. 3 with miRNAs of Set No. 5 and Set No. 8, etc.

[0094] As mentioned above, an expression profile of a miRNA or of a set (signature) comprising, essentially consisting of, or consisting of at least 2 miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, is determined in the first step of the method of the present invention, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of

- (i) a nucleotide sequence according to SEQ ID NO: 1 to SEQ ID NO: 283,
- (ii) a nucleotide sequence that is a fragment of the nucleotide sequence according to (i), preferably, a nucleotide sequence that is a fragment which is between 1 and 12, more preferably between 1 and 8, and most preferably between 1 and 5 or 1 and 3, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, nucleotides shorter than the nucleotide sequence according to (i), and
- (iii) a nucleotide sequence that has at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% or 99%, i.e. 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%,

sequence identity to the nucleotide sequence according to (i) or nucleotide sequence fragment according to (ii).

[0095] Further, as mentioned above, it is preferred that an expression profile of a miRNA or of a set (signature) comprising, essentially consisting of, or consisting of at least 2, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, or 152 miRNAs, or comprising/consisting of 153 miRNAs representative for an acute coronary syndrome in a blood sample, and more preferably comprising at least one further miRNA (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 further miRNA(s)) representative for an acute coronary syndrome in a blood sample, is determined in the first step of the method of the present invention, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of

(i) a nucleotide sequence according to SEQ ID NO: 1 to SEQ ID NO: 153,

(ii) a nucleotide sequence that is a fragment of the nucleotide sequence according to (i), preferably, a nucleotide sequence that is a fragment which is between 1 and 12, more preferably between 1 and 8, and most preferably between 1 and 5 or 1 and 3, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, nucleotides shorter than the nucleotide sequence according to (i), and

(iii) a nucleotide sequence that has at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% or 99%, i.e. 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%, sequence identity to the nucleotide sequence according to (i) or nucleotide sequence fragment according to (ii), and wherein the nucleotide sequence of the at least one further miRNA comprised in the set is selected from the group consisting of

(i) a nucleotide sequence according to SEQ ID NO: 154 to SEQ ID NO: 241,

(ii) a nucleotide sequence that is a fragment of the nucleotide sequence according to (i), preferably, a nucleotide sequence that is a fragment which is between 1 and 12, more preferably between 1 and 8, and most preferably between 1 and 5 or 1 and 3, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, nucleotides shorter than the nucleotide sequence according to (i), and

(iii) a nucleotide sequence that has at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% or 99%, i.e. 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%, sequence identity to the nucleotide sequence according to (i) or nucleotide sequence fragment according to (ii).

[0096] It is particularly preferred that the nucleotide sequence as defined in (iii) has at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% or 99%, i.e. 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%, sequence identity over a continuous stretch of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more nucleotides, preferably over the whole length, to the nucleotide sequence of the nucleotide according to (i) or nucleotide fragment according to (ii).

[0097] In addition, the nucleotide sequence as defined in (ii) (i.e. nucleotide sequence fragment) or (iii) (i.e. nucleotide sequence variant or nucleotide sequence fragment variant) is only regarded as a nucleotide sequence as defined in (ii) (i.e. nucleotide sequence fragment) or (iii) (i.e. nucleotide sequence variant or nucleotide sequence fragment variant) within the context of the present invention, if it can still be bound, hybridized, recognized, or detected by a polynucleotide (probe) of complementary sequence, e.g. a polynucleotide (probe) which is complementary to the respective nucleotide sequence as defined in (i), through one or more types of chemical bonds, usually through complementary base pairing, usually through hydrogen bond formation under stringent hybridization conditions. The skilled person can readily assess whether a nucleotide sequence as defined in (ii) (i.e. nucleotide sequence fragment) or (iii) (i.e. nucleotide sequence variant or nucleotide sequence fragment variant) can still be bound, hybridized, recognized, or detected by a polynucleotide (probe) of complementary sequence, e.g. a polynucleotide (probe) which is complementary to the respective nucleotide sequence as defined in (i). Suitable assays to determine whether hybridization under stringent conditions still occurs are well known in the art. However, as an example, a suitable assay to determine whether hybridization still occurs comprises the steps of: (a) incubating a nucleotide sequence as defined in (ii) or (iii) labelled with biotin with a polynucleotide (probe) of complementary sequence, e.g. a polynucleotide (probe) which is complementary to the respective nucleotide sequence as defined in (i), wherein the polynucleotide (probe) is attached onto a biochip, under

stringent hybridization conditions, (b) washing the biochip to remove unspecific bindings, (c) subjecting the biochip to a detection system, and (c) analyzing whether the nucleotide sequence can still be hybridized or detected by a polynucleotide (probe) of complementary sequence, e.g. a polynucleotide (probe) which is complementary to the respective nucleotide sequence as defined in (i). As a positive control, the respective miRNA as defined in (i) may be used. Preferably stringent hybridization conditions include the following: 50% formamide, 5x SSC, and 1% SDS, incubating at 42°C, or, 5x SSC, 1% SDS, incubating at 65°C, with wash in 0.2x SSC, and 0.1% SDS at 65°C; or 6x SSPE, 10 % formamide, 0.01 %, Tween 20, 0.1 x TE buffer, 0.5 mg/ml BSA, 0.1 mg/ml herring sperm DNA, incubating at 42°C with wash in 0.5x SSPE and 6x SSPE at 45°C.

[0098] In preferred embodiments of the method of the present invention, an expression profile of a miRNA selected from the group consisting of SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a), or selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 10 is determined in step (i). It is particularly preferred embodiment of the method of the present invention, the miRNAs of which the expression profile is determined has the SEQ ID NO: 1 (hsa-miR-1291).

[0099] In other preferred embodiments of the method of the present invention, an expression profile of a miRNA listed in Figure 29 is determined in step (i).

[0100] It is preferred that in step (i) of the method of the present invention, a polynucleotide according to the present invention is used for determining an expression profile of a miRNA representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, particularly of SEQ ID NO: 1 to SEQ ID NO: 153. It is particularly preferred that the nucleotide sequence of said miRNA is selected from the list of Figure 29.

[0101] Preferably, the polynucleotide according to the present invention is used for determining an expression profile of a miRNA representative for an acute coronary syndrome in a blood sample from a human, wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a), or selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 10. It is particularly preferred that said polynucleotide used for determining an expression profile of a miRNA representative for an acute coronary syndrome in a blood sample from a human is complementary to the sequence of the miRNAs which are selected from the group consisting of SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a), or selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 10. It is mostly preferred that the polynucleotide is in single stranded form and attached to a solid support, substrate, surface, platform or matrix, e.g. biochip, and is incubated with a miRNA of complementary sequence, wherein said miRNA is selected from the group consisting of SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a), or selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 10, for determining an expression profile of said miRNA.

[0102] It is also preferred that in step (i) of the method of the present invention, a set comprising at least two polynucleotides according to the present invention is used for determining an expression profile of a set (signature) comprising at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, particularly of SEQ ID NO: 1 to SEQ ID NO: 153. Preferably, the nucleotide sequences of said miRNAs are selected from one or more sets listed in Figure 28 and/or Figure 30.

[0103] It is particularly preferred that in step (i) of the method of the present invention, a set comprising at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153 polynucleotides according to the present invention is used for determining an expression profile of a set (signature) comprising at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110,

111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153 miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153; and wherein said preferred set of polynucleotides used in step (i) of the method of the present invention preferably comprises at least one further polynucleotide (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 polynucleotide(s)) according to the present invention for determining an expression profile of at least one further miRNA (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 miRNA(s)) comprised in the above-mentioned set (signature) of miRNAs, wherein the nucleotide sequence of the at least one further miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241.

[0104] It is further particularly preferred that in step (i) of the method of the present invention, a set comprising at least 10 polynucleotides according to the invention is used for determining an expression profile of a set comprising at least 10 miRNAs representative for an acute coronary syndrome in a blood sample from a human, wherein the nucleotide sequences of the at least 10 miRNAs comprised in the set have SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a), or have SEQ ID NO: 1 to SEQ ID NO: 10. It is also particularly preferred that the at least 10 polynucleotides according to the invention which are comprised in the set used for determining an expression profile of a set comprising at least 10 miRNAs representative for an acute coronary syndrome in a blood sample from a human are complementary to the sequences of said miRNAs, wherein the nucleotide sequences of the at least 10 miRNAs comprised in the set have SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a), or have SEQ ID NO: 1 to SEQ ID NO: 10. It is mostly preferred that the at least 10 polynucleotides according to the invention which are comprised in the set used for determining an expression profile of a set comprising at least 10 miRNAs representative for an acute coronary syndrome in a blood sample from a human are in single stranded form and attached to a solid surface, support, or matrix, e.g. biochip, and are incubated with said miRNAs of complementary sequence, wherein the nucleotide sequences of the at least 10 miRNAs comprised in the set have SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a), or have SEQ ID NO: 1 to SEQ ID NO: 10, for determining an expression profile of said miRNA.

[0105] In a preferred embodiment, the blood sample from a human is whole blood or a blood fraction such as serum or plasma. Blood cells also known as hemopoietic cells may also be used, e.g. erythrocytes, leukocytes and/or thrombocytes. Human blood samples may be collected by any convenient method, as known in the art. It is preferred that 0.1 to 20 ml blood, preferably 0.5 to 10 ml blood, i.e. 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 ml blood, is collected. In another preferred embodiment, the blood sample is obtained from a human prior to initiation of therapeutic treatment, during therapeutic treatment and/or after therapeutic treatment. It is particularly preferred that total RNA or subfractions thereof including the miRNA is isolated, e.g. extracted, from the human blood sample in order to determine the expression profile of a miRNA or miRNAs comprised in the blood sample of a human.

[0106] The inventors of the present invention surprisingly found that miRNAs are not only present in a blood sample but also that miRNAs remain stable and that, thus, blood miRNAs can be used as biomarkers for detecting and/or prognosis of an acute coronary syndrome in humans. Furthermore, the inventors found that the miRNAs present in blood are different from the ones found in heart tissue of an individual suffering from an acute coronary syndrome. Therefore, the use of blood samples in the method of the present invention for detection and/or prognosis of an acute coronary syndrome has a number of advantage, for example, blood miRNAs have a high sensitivity, blood is relatively easy to obtain and even can be collected via routine physical examination, the costs for detection are low, and the samples can easily be preserved (e.g. at - 20°C). Further, blood circulates to all tissues in the body and, therefore, blood is able to reflect the physiological pathology of the whole organism and the detection of blood miRNAs results in an indicator of human health, and according to the present invention, as an indication whether a person suffers from an acute coronary syndrome. Furthermore, this method can widely be used in general survey of an acute coronary syndrome. Moreover, the inventors of the present invention surprisingly found that blood is an efficient mean for early diagnosis of an acute coronary syndrome. As novel disease markers, blood miRNAs improve the low-specificity and low-sensitivity caused by

individual differences which other markers are difficult to overcome, and notable increase the clinical detection rate of an acute coronary syndrome so as to realize early diagnosis of an acute coronary syndrome.

[0107] Furthermore, according to the present invention, a first diagnosis of an acute coronary syndrome can be performed employing, as disclosed, miRNA-detection in blood, followed by a second diagnosis that is based on other methods (e.g. other biomarkers, miRNA-markers in heart tissue, and/or imaging methods).

[0108] As mentioned above, in step (i) of the method of the present invention, an expression profile of a miRNA or set comprising at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, is determined. This determination may be carried out by any convenient means for determining the expression level of a nucleotide sequence such as miRNA. For expression profiling, qualitative, semi-quantitative and preferably quantitative detection methods can be used. A variety of techniques are well known to the person skilled in the art. It is preferred that an expression profile of the miRNA(s) representative for an acute coronary syndrome is determined by nucleic acid hybridization, nucleic acid amplification, polymerase extension, sequencing, mass spectroscopy, or any combination thereof.

[0109] Nucleic acid amplification may be performed using real time polymerase chain reaction (RT-PCR) such as real time quantitative PCR (RT qPCR). This technique is suitable for detecting the expression profile of single miRNAs. It is particularly suitable for detecting low abandoned miRNAs. The real time quantitative PCR (RT qPCR) allows the analysis of a single miRNA as well as a complex set of miRNAs comprised in a blood sample of a human, e.g. a single miRNA or a set comprising at least two miRNAs, wherein the nucleotide sequence of said miRNA or said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153 (e.g. a set of 153 miRNAs having SEQ ID NO: 1 to SEQ ID NO: 153), and wherein optionally the nucleotide sequence of at least one further miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241 (e.g. set of 241 miRNAs having SEQ ID NO: 1 to SEQ ID NO: 241). The real time polymerase chain reaction (RT-PCR) such as real time quantitative PCR (RT qPCR) technique, however, is preferred for the analysis of single miRNAs or set comprising a low number of miRNAs (e.g. 2 to 50 miRNAs). It is particularly suitable for detecting low abandoned miRNAs.

[0110] The aforesaid real time polymerase chain reaction (RT-PCR) may include the following steps: (i) extracting the total RNA from the blood sample, e.g. whole blood, serum, or plasma, of a human with unknown clinical condition, e.g. healthy person or patient suffering from an acute coronary syndrome, and obtaining cDNA samples by RNA reverse transcription (RT) reaction using miRNA-specific primers; or collecting blood sample, e.g. whole blood, serum, or plasma, from a human and conducting reverse transcriptase reaction using miRNA-specific primers with blood, e.g. whole blood, serum, or plasma, being a puffer so as to prepare cDNA samples, (ii) designing miRNA-specific cDNA forward primers and providing universal reverse primers to amplify the cDNA via polymerase chain reaction (PCR), (iii) adding a fluorescent probe to conduct PCR, and (iv) detecting and comparing the variation in levels of miRNAs in the blood sample, e.g. whole blood, serum, or plasma, relative to those of miRNAs in normal (control) blood, e.g. whole blood, serum, or plasma, sample.

[0111] A variety of kits and protocols to determine an expression profile by real time polymerase chain reaction (RT-PCR) such as real time quantitative PCR (RT qPCR) are available. For example, reverse transcription of miRNAs may be performed using the TaqMan MicroRNA Reverse Transcription Kit (Applied Biosystems) according to manufacturer's recommendations. Briefly, miRNA may be combined with dNTPs, MultiScribe reverse transcriptase and the primer specific for the target miRNA. The resulting cDNA may be diluted and may be used for PCR reaction. The PCR may be performed according to the manufacturer's recommendation (Applied Biosystems). Briefly, cDNA may be combined with the TaqMan assay specific for the target miRNA and PCR reaction may be performed using ABI7300.

[0112] Furthermore, according to the present invention, the miRNA or the set comprising at least two miRNAs for diagnosing and/or prognosing of an acute coronary syndrome in a blood sample from a human, particularly human patient, may be established on one experimental platform (e.g. microarray), while for routine diagnosis/prognosis another experimental platform (e.g.. qPCR) may be chosen.

[0113] Nucleic acid hybridization may be performed using a microarray/biochip, or *in situ* hybridization. The microarray/biochip allows the analysis of a single miRNA as well as a complex set of miRNAs comprised in a blood sample of a human, particularly human patient, e.g. a single miRNA or a set comprising at least two miRNAs, wherein the nucleotide sequence of said miRNA or said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153 (e.g. a set of 153 miRNAs having SEQ ID NO: 1 to SEQ ID NO: 153), and wherein optionally the nucleotide sequence of at least one further miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241 (e.g. set of 241 miRNAs having SEQ ID NO: 1 to SEQ ID NO: 241). The microarray/biochip, however, is preferred for the analysis of complex sets of miRNAs (e.g. sets of 50, 100, 150, 200, or more miRNAs). For nucleic acid hybridization, for example, the polynucleotides (probes) according to the present invention with complementarity to the corresponding miRNA(s) to be detected are attached to a solid phase to generate a microarray/biochip (e.g. 153 polynucleotides (probes) which are complementary to the 153 miRNAs having SEQ ID NO: 1 to SEQ ID NO: 153 comprised in a set). Said microarray/biochip is then incubated with miRNAs, isolated (e.g. extracted) from the human blood sample, which may be labelled (Figures 8, 9), e.g. fluorescently labelled, or unlabelled (Figures 10, 11). Upon hybridization of the labelled miRNAs to

the complementary polynucleotide sequences on the microarray/biochip, the success of hybridisation may be controlled and the intensity of hybridization may be determined via the hybridisation signal of the label in order to determine the expression level of each tested miRNA in said blood probe. Examples of preferred hybridization assays are shown in Figures 8 to 11.

[0114] Thus, it is preferred that in step (i) of the method of the present invention, an expression profile of a set comprising at least two miRNAs representative for an acute coronary syndrome is determined by nucleic acid hybridization using a microarray/biochip which comprises a set comprising at least two polynucleotides (probes) that are complementary to the miRNAs, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283.

[0115] It is particularly preferred that in step (i) of the method of the present invention, an expression profile of a set comprising at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153 miRNAs representative for an acute coronary syndrome is determined by nucleic acid hybridization using a microarray/biochip which comprises a set comprising at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153 polynucleotides (probes) that are complementary to the miRNAs, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153.

Preferably, said biochip comprises the set of polynucleotides as mentioned above and comprises at least one further polynucleotide (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 polynucleotide(s)) according to the invention for determining an expression profile of at least one further miRNA (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 miRNA(s)) comprised in the set of miRNAs, wherein the nucleotide sequence of the at least one further miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241.

[0116] It is also particularly preferred that in step (i) of the method of the present invention, an expression profile of a set comprising at least 10 miRNAs representative for an acute coronary syndrome is determined by nucleic acid hybridization using a microarray/biochip which comprises a set comprising at least 10 polynucleotides (probes) that are complementary to the miRNAs, wherein the nucleotide sequences of the at least 10 miRNAs comprised in the set have SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsamiR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a), or have SEQ ID NO: 1 to SEQ ID NO: 10. It is further particularly preferred that in step (i) of the method of the present invention, an expression profile of a set comprising at least 50 miRNAs representative for an acute coronary syndrome is determined by nucleic acid hybridization using a microarray/biochip which comprises a set comprising at least 50 polynucleotides (probes) that are complementary to the miRNAs, wherein the nucleotide sequences of the at least 50 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 50. It is mostly preferred that in step (i) of the method of the present invention, an expression profile of a set comprising at least 80 miRNAs representative for an acute coronary syndrome is determined by nucleic acid hybridization using a microarray/biochip which comprises a set comprising at least 80 polynucleotides (probes) that are complementary to the miRNAs, wherein the nucleotide sequences of the at least 80 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 80. It is also mostly preferred that in step (i) of the method of the present invention, an expression profile of a set comprising at least 100 miRNAs representative for an acute coronary syndrome is determined by nucleic acid hybridization using a microarray/biochip which comprises a set comprising at least 100 polynucleotides (probes) that are complementary to the miRNAs, wherein the nucleotide sequences of the at least 100 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 100.

[0117] As already mentioned above, the method of the present invention may comprise, as a first alternative, the following second step:

(ii) comparing said expression profile to a reference, wherein the comparison of said expression profile to said

reference allows for the diagnosis and/or prognosis of an acute coronary syndrome.

[0118] Thus, subsequent to the determination of an expression profile of a miRNA as defined above or a set comprising at least two miRNAs as defined above in a blood sample from a human, particularly human patient, (step (i)), the method of the present invention further comprises the step of comparing said expression profile to a reference, wherein the comparison of said expression profile to said reference allows for the diagnosis and/or prognosis of an acute coronary syndrome (step (ii)).

[0119] The human, particularly human patient, to be diagnosed with the method of the present invention for an acute coronary syndrome (e.g. myocardial infarction such as non-ST segment elevation myocardial infarction or ST segment elevation myocardial infarction, or Unstable angina (UA)) may be a healthy or may be diseased, e.g. suffer from an acute coronary syndrome (e.g. myocardial infarction or Unstable angina (UA)) or suffer from another disease not tested/known. The human to be diagnosed with the method of the present invention may suffer from a specific type of myocardial infarction, namely from non-ST segment elevation myocardial infarction (NSTEMI), or from ST segment elevation myocardial infarction (STEMI). It is also possible to determine, whether the human to be diagnosed will develop the above-mentioned syndrome as the inventors of the present invention surprisingly found that miRNAs representative for an acute coronary syndrome are already present in the blood before an acute coronary syndrome occurs or during the early stage of myocardial injury.

[0120] The reference may be any reference which allows for the diagnosis and/or prognosis of an acute coronary syndrome, e.g. indicated reference data or value(s).

[0121] The reference may be the reference expression profile of the same single miRNA or set of miRNAs selected in step (i) in a blood sample, preferably originated from the same source (e.g. serum, plasma, or blood cells) as the blood sample from the human, particularly human patient, to be tested, but obtained from a person known to be healthy. The reference may also be the reference expression profile of the same single miRNA or set of miRNAs selected in step (i) in a blood sample, preferably originated from the same source as the blood sample from the human, particularly human patient, to be tested, but obtained from a patient known to suffer from an acute coronary syndrome (e.g. myocardial infarction such as non-ST segment elevation myocardial infarction or ST segment elevation myocardial infarction, or Unstable angina (UA), or the like). Further, the reference may be the reference profiles of the same single miRNA or set of miRNAs selected in step (i) in a blood sample, preferably originated from the same source as the blood sample from the human, particularly human patient, to be tested, but obtained from a person known to be healthy and from a patient known to suffer from an acute coronary syndrome (e.g. myocardial infarction such as non-ST segment elevation myocardial infarction or ST segment elevation myocardial infarction, or Unstable angina (UA), or the like).

[0122] As to the single miRNA or set of miRNAs, that means in other words that the reference expression profile is the profile of a single miRNA that has a nucleotide sequence that corresponds (is identical) to the nucleotide sequence selected in step (i) or is the profile of a set comprising at least two miRNAs that have nucleotide sequences that correspond (are identical) to the nucleotide sequences in step (i) but obtained from a healthy person or patient known to suffer from an acute coronary syndrome (e.g. myocardial infarction such as non-ST segment elevation myocardial infarction or ST segment elevation myocardial infarction, or Unstable angina (UA)).

[0123] Preferably, both the reference expression profile of the reference and the expression profile of the above step (i) are determined in a blood serum sample, blood plasma sample or in a sample of blood cells (e.g. erythrocytes, leukocytes and/or thrombocytes). It is understood that the reference expression profile of the reference is not necessarily obtained from a single person (e.g. healthy or diseased person) but may be an average expression profile of a plurality of persons (e.g. healthy or diseased persons), preferably 2 to 40 persons, more preferably 10 to 25 persons, and most preferably 15 to 20 persons, e.g. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 persons. Preferably, the reference expression profile of the reference is obtained from a person of the same gender (e.g. female or male) and/or of a similar age/phase of life (e.g. infant, young children, juvenile, or adult) as the person to be tested or diagnosed.

[0124] The comparison of the expression profile of the human to be diagnosed to said reference, e.g. reference expression profile of at least one human, preferably 10 to 40 humans, more preferably 15 to 25 humans, known to be healthy, then allows for the diagnosis and/or prognosis of an acute coronary syndrome (step (ii)). For example, if two selected miRNAs in the expression profile of a human to be diagnosed for an acute coronary syndrome are down-regulated and if the two selected miRNAs in the reference expression profile of a person known to suffer from an acute coronary syndrome are up-regulated, the person tested is healthy, i.e. the person does not suffer from an acute coronary syndrome. In the converse case, if two selected miRNAs in the expression profile of a human to be diagnosed for an acute coronary syndrome are up-regulated and if the two selected miRNAs in the reference expression profile of a person known to suffer from an acute coronary syndrome are also up-regulated, particularly with the same level, the person tested is diseased, i.e. the person suffers from an acute coronary syndrome. It should be noted that a person that is diagnosed as being healthy, i.e. not suffering from an acute coronary syndrome, may possibly suffer from another disease not tested/known.

[0125] In preferred embodiments of the method of the present invention, the reference is obtained from a reference expression profile of at least one person, particularly human, preferably 2 to 40 persons, particularly humans, more preferably 10 to 25 persons, particularly humans, and most preferably 15 to 20 persons, particularly humans, e.g. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 persons, particularly humans, known to be healthy or diseased (i.e. suffering from an acute coronary syndrome (e.g. myocardial infarction such as non-ST segment elevation myocardial infarction or ST segment elevation myocardial infarction, or Unstable angina (UA)), wherein the reference expression profile is the profile of a single miRNA that has a nucleotide sequence that corresponds (is identical) to the nucleotide sequence selected in step (i) (e.g. miRNA according to SEQ ID NO: 1) or is the profile of a set comprising at least two miRNAs that have nucleotide sequences that correspond (are identical) to the nucleotide sequence selected in step (i) (e.g. miRNAs according to SEQ ID NO: 1 to SEQ ID NO: 10) of the method of the present invention.

[0126] More preferably, the reference is obtained from reference expression profiles of at least two humans, preferably 3 to 40 humans, more preferably 10 to 25 humans, and most preferably 15 to 20 humans, e.g. 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 humans, with at least two known clinical conditions, preferably 2 to 5, more preferably 2 or 3, from which at least one, e.g. 1, 2, 3, or 4, is an acute coronary syndrome (e.g. myocardial infarction such as non-ST segment elevation myocardial infarction or ST segment elevation myocardial infarction, or Unstable angina (UA)), wherein the reference expression profiles are the profiles of a single miRNA that has a nucleotide sequence that corresponds to the nucleotide sequence selected in step (i) or are the profiles of a set comprising at least two miRNAs that have nucleotide sequences that correspond to the nucleotide sequences selected in step (i).

[0127] The term "(clinical) condition" (biological state or health state) means a status of a subject that can be described by physical, mental or social criteria. It includes as well so-called "healthy" and "diseased" conditions. For the definition of called "healthy" and "diseased" conditions it is referred to the international classification of diseases (ICD) of the WHO (<http://www.int.classifications/icd/en/index.html>). When two or more conditions are compared according to a preferred embodiment of the method of the present invention, it is understood that this is possible for all conditions that can be defined and is not limited to a comparison of a diseased versus healthy comparison and extends to multiway comparison, under the condition that at least one condition is an acute coronary syndrome, e.g. myocardial infarction such as non-ST segment elevation myocardial infarction or ST segment elevation myocardial infarction, or Unstable angina (UA).

[0128] Examples of comparison are, but are not limited to:

- Diagnosis/Prognosis within acute coronary syndromes encompass for example
 - (i) Unstable angina pectoris versus healthy control,
 - (ii) acute myocardial infarction versus healthy control,
 - (iii) Unstable angina pectoris versus acute myocardial infarction, or
 - (iv) non-ST segment elevation myocardial infarction (NSTEMI) versus ST segment elevation myocardial infarction (STEMI).
- Diagnosis/Prognosis of acute coronary syndrome versus other heart diseases, for example
 - (i) Acute myocardial infarction versus heart failure,
 - (ii) Acute myocardial infarction versus cardiomyopathy,
 - (iii) Acute myocardial infarction versus coronary heart disease, or
 - (iv) unstable angina pectoris versus stable angina pectoris.
- Diagnosis/Prognosis of acute coronary syndrome versus other diseases, for example,
 - (i) Acute myocardial infarction versus cardiovascular disease,
 - (ii) acute coronary syndrome versus lung cancer,
 - (iii) acute coronary syndromes versus arteriosclerosis, or
 - (iv) acute coronary syndromes versus multiple sclerosis.

[0129] Thus, for example, the reference may be obtained from reference expression profiles of at least two humans, one human suffering from an acute coronary syndrome and one being healthy, i.e. not suffering from an acute coronary syndrome, wherein the reference expression profiles are the profiles of a single miRNA that has a nucleotide sequence that corresponds to the nucleotide sequence selected in step (i) or are the profiles of a set comprising at least two miRNAs that have nucleotide sequences that correspond to the nucleotide sequences selected in step (i). The comparison of the expression profile of the human to be diagnosed to said reference, may then allow for the diagnosis and/or

prognosis of an acute coronary syndrome (step (ii)), either the human to be diagnosed is healthy, i.e. not suffering from an acute coronary syndrome, or diseased, i.e. suffering from an acute coronary syndrome.

[0130] The reference may also be obtained from reference expression profiles of at least two humans, one human suffering from myocardial infarction, e.g. non-ST segment elevation myocardial infarction or ST segment elevation myocardial infarction, and one suffering from Unstable angina (UA), wherein the reference expression profiles are the profiles of a single miRNA that has a nucleotide sequence that corresponds to the nucleotide sequence selected in step (i) or are the profiles of a set comprising at least two miRNAs that have nucleotide sequences that correspond to the nucleotide sequences selected in step (i). The comparison of the expression profile of the human to be diagnosed to said reference, may then allow whether the human to be diagnosed suffers from myocardial infarction or Unstable angina (UA).

[0131] The reference may also be obtained from reference expression profiles of at least three humans, one human suffering from an acute coronary syndrome, one suffering from cardiomyopathy, and one being healthy, wherein the reference expression profiles are the profiles of a single miRNA that has a nucleotide sequence that corresponds to the nucleotide sequence selected in step (i) or are the profiles of a set comprising at least two miRNAs that have nucleotide sequences that correspond to the nucleotide sequences selected in step (i). The comparison of the expression profile of the human to be diagnosed to said reference, may also allow to decide whether the human suffers from an acute coronary syndrome.

[0132] It is understood that the reference expression profiles of the reference are not necessarily obtained from a single human (e.g. healthy or diseased human) but may be average expression profiles of a plurality of humans (e.g. healthy or diseased humans), preferably 2 to 40 persons, more preferably 10 to 25 persons, and most preferably 15 to 20 persons, e.g. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 persons. Preferably, the reference expression profiles of the reference are obtained from a person of the same gender (e.g. female or male) and/or of a similar age/phase of life (e.g. infant, young children, juvenile, or adult) as the person to be tested or diagnosed.

[0133] Preferably, the reference is obtained from reference profiles of the same number of humans. For example, the reference may be obtained from reference profiles of 10 humans being healthy and 10 humans suffering from an acute coronary syndrome. The reference may be also obtained from reference profiles of 20 humans being healthy, 20 humans suffering from an acute coronary syndrome and 20 humans suffering from cardiomyopathy.

[0134] The inventors of the present invention surprisingly found that the application of a machine learning approach (e.g. t-test, AUC, support vector machine, hierarchical clustering, or k-means) allows a better discrimination between two (or more) clinical conditions, e.g. healthy and suffering from an acute coronary syndrome, for a defined set of miRNA biomarkers. The application of this approach namely leads to an algorithm that is trained by reference data (i.e. data of reference miRNA expression profiles from the two clinical conditions, e.g. healthy and suffering from an acute coronary syndrome, for the defined set of miRNA markers) to discriminate between the two (or more) statistical classes (i.e. two clinical conditions, e.g. healthy or suffering from an acute coronary syndrome). In this way, the performance for diagnosing/prognosing of individuals suffering from an acute coronary syndrome can be increased (see also experimental section for details).

[0135] Thus, most preferably, the comparison to the reference comprises the application of an algorithm or mathematical function. It is preferred that the algorithm or mathematical function is obtained using a machine learning approach. Machine learning approaches, may include but are not restricted to supervised or unsupervised analysis: classification techniques (e.g. naive Bayes, Linear Discriminant Analysis, Quadratic Discriminant Analysis Neural Nets, Tree based approaches, Support Vector Machines, Nearest Neighbour Approaches), Regression techniques (e.g. linear Regression, Multiple Regression, logistic regression, probit regression, ordinal logistic regression ordinal Probit-Regression, Poisson Regression, negative binomial Regression, multinomial logistic Regression, truncated regression), Clustering techniques (e.g. k-means clustering, hierarchical clustering, PCA), Adaptations, extensions, and combinations of the previously mentioned approaches.

[0136] For example, the machine learning approach may be applied to the reference expression profile data of a set comprising at least 2 miRNAs (e.g. 10 miRNAs such as miRNAs according to SEQ ID NO: 1 to 10) of a human known to suffer from an acute coronary syndrome and of a human known to be healthy and may lead to the obtainment of an algorithm or mathematical function. This algorithm or mathematical function may then be applied to a miRNA expression profile of the same at least 2 miRNAs as mentioned above (e.g. 10 miRNAs such as miRNAs according to SEQ ID NO: 1 to 10) of a human to be diagnosed for an acute coronary syndrome and, thus, may then allow to discriminate whether the human to be tested is healthy, i.e. not suffering from an acute coronary syndrome, or diseased, i.e. suffering from an acute coronary syndrome.

[0137] In another preferred embodiment of the method of the present invention, the reference is a reference expression profile (data) of at least one subject, preferably the reference is an average expression profile (data) of at least 2 to 40 subjects, more preferably of at least 10 to 25 subjects, and most preferably of at least 15 to 20 subjects, e.g. of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35,

36, 37, 38, 39, or 40 subjects, with one known clinical condition which is an acute coronary syndrome, or which is no acute coronary syndrome (i.e. healthy/healthiness), wherein the reference expression profile is the profile of a (single) miRNA that has a nucleotide sequence that essentially corresponds (is essentially identical), preferably that corresponds (is identical), to the nucleotide sequence of the miRNA of step (i) or is the profile of a set comprising at least two miRNAs that have nucleotide sequences that essentially correspond (are essentially identical), preferably that correspond (are identical), to the nucleotide sequences of the miRNAs of step (i). It should be noted that said subject(s) is (are) human(s). Said subject(s) may also be designated as control subject(s).

[0138] For example, said reference may be a reference expression profile of at least one subject known to be not affected by an acute coronary syndrome (i.e. healthy) or known to be affected by an acute coronary syndrome (i.e. diseased), wherein the reference expression profile is the profile of a single miRNA that has a nucleotide sequence that essentially corresponds (is essentially identical), preferably that corresponds (is identical), to the nucleotide sequence of the miRNA of step (i) or is the profile of a set comprising at least two miRNAs that have nucleotide sequences that essentially correspond (are essentially identical), preferably that correspond (are identical), to the nucleotide sequences of the miRNAs of step (i).

[0139] The terms "essentially correspond(s)" or "essentially identical", as used in this aspect of the present invention, mean that the miRNA(s) of step (i) and the miRNA(s) of the reference expression profile may slightly differ in their nucleotide sequence, whereas said difference is so marginal that it may still allow for the diagnosis and/or prognosis of an acute coronary syndrome. Preferably, the nucleotide sequence(s) of the miRNA(s) of step (i) and the nucleotide sequence(s) of the miRNA(s) of the reference expression profile differ in 1 to 5, more preferably in 1 to 3, and most preferably in 1 to 2 nucleotides, i.e. in 1, 2, 3, 4, or 5 nucleotides. It is preferred that said difference resides in 1 to 5, more preferably 1 to 3, and most preferably 1 to 2 nucleotide mutations, i.e. 1, 2, 3, 4, or 5 nucleotide mutations (e.g. substitutions, additions, insertions, and/or deletions). This is caused by the fact that the miRNAs within the human species may differ. It is preferred that the miRNA(s) of step (i) and the miRNA(s) of the reference expression profile do not differ in their nucleotide sequence, i.e. are identical. It is particularly preferred that the miRNA(s) of step (i) and the miRNA(s) of the reference expression profile are derived from subject/patients of the same gender (e.g. female or male) and/or similar age/phase of life (e.g. infant, young children, juvenile, or adult).

[0140] The comparison of the expression profile of the human, particularly human patient, to be diagnosed and/or prognosed to the (average) reference expression profile (data), may then allow for diagnosing and/or prognosing of an acute coronary syndrome (step (ii)).

[0141] Considering the above, diagnosing preferably means comparing the expression profile (data) of a human, particularly human patient, determined in step (i) to the (average) reference expression profile (data) as mentioned above to decide, if the at least one known clinical condition, which is an acute coronary syndrome, or which is no acute coronary syndrome (i.e. healthy), is present in said human, particularly human patient. Prognosing preferably means comparing the expression profile (data) of a human, particularly human patient, determined in step (i) to the (average) reference expression profile (data) as mentioned above to decide, if the at least one known clinical condition, which is an acute coronary syndrome, or which is no acute coronary syndrome (i.e. healthy), will likely be present in said human, particularly human patient.

[0142] For example, the human, particularly human patient, may be diagnosed as not suffering from an acute coronary syndrome (i.e. being healthy), or as suffering from an acute coronary syndrome (i.e. being diseased). Further, for example, the human, particularly human patient, may be prognosed as not developing an acute coronary syndrome (i.e. staying healthy), or as developing an acute coronary syndrome (i.e. getting diseased).

[0143] Diagnosing/prognosing of an acute coronary syndrome based on (a) reference expression profile (data) as reference may take place as follows: For instance, (i) if the miRNA(s) of step (i) (e.g. a single miRNA or a set of at least 2 miRNAs) in the expression profile of a human, particularly human patient, to be diagnosed for an acute coronary syndrome is (are), for example, at least 2 fold higher (up-regulated) compared to said miRNA(s) (e.g. a single miRNA or a set of at least 2 miRNAs) in the reference expression profile of a human subject known not to suffer from an acute coronary syndrome (i.e. being healthy), the human, particularly human patient, tested is diagnosed as suffering from an acute coronary syndrome (i.e. being diseased) or prognosed as likely developing an acute coronary syndrome (i.e. getting diseased), or (ii) if the miRNA(s) of step (i) (e.g. a single miRNA or a set of 2 miRNAs) in the expression profile of a human, particularly human patient, to be diagnosed for an acute coronary syndrome is (are), for example, at least 2 fold lower (down-regulated) compared to said miRNA(s) (e.g. a single miRNA or a set of at least 2 miRNAs) in the reference expression profile of a human subject known not to suffer from an acute coronary syndrome (i.e. being healthy), the human, particularly human patient, tested is diagnosed as suffering from an acute coronary syndrome (i.e. being diseased) or prognosed as likely developing an acute coronary syndrome (i.e. getting diseased).

[0144] In the converse case, (i) if the miRNA(s) of step (i) (e.g. a single miRNA or a set of at least 2 miRNAs) in the expression profile of a human, particularly human patient, to be diagnosed for an acute coronary syndrome is (are), for example, not at least 2 fold higher (up-regulated) compared to said miRNA(s) (e.g. a single miRNA or a set of at least 2 miRNAs) in the reference expression profile of a human subject known not to suffer from an acute coronary syndrome

(i.e. being healthy), the human, particularly human patient, tested is diagnosed as not suffering from an acute coronary syndrome (i.e. being healthy) or prognosed as likely not developing an acute coronary syndrome (i.e. staying healthy), or (ii) if the miRNA(s) of step (i) (e.g. a single miRNA or a set of 2 miRNAs) in the expression profile of a human, particularly human patient, to be diagnosed for an acute coronary syndrome is (are), for example, not at least 2 fold lower (down-regulated) compared to said miRNA(s) (e.g. a single miRNA or a set of at least 2 miRNAs) in the reference expression profile of a human subject known not to suffer from an acute coronary syndrome (i.e. being healthy), the human, particularly human patient, tested is diagnosed as not suffering from an acute coronary syndrome (i.e. being healthy) or prognosed as likely not developing an acute coronary syndrome (i.e. staying healthy).

[0145] It should be noted that a human, particularly human patient, that is diagnosed as being healthy, i.e. not suffering from an acute coronary syndrome, may possibly suffer from another disease not tested/known, or a human, particularly human patient, that is prognosed as staying healthy, i.e. as likely not developing an acute coronary syndrome, may possibly develop another disease not tested/known.

[0146] As already mentioned above, the method of the present invention may comprise, as a second alternative, the following second step:

(ii) applying an algorithm or a mathematical function to said expression profile, wherein the application of said algorithm or mathematical function to said expression profile allows for the diagnosis and/or prognosis of an acute coronary syndrome.

[0147] Thus, subsequent to the determination of an expression profile (data) of a (single) miRNA representative for an acute coronary syndrome as defined above, or of a set comprising at least two miRNAs representative for an acute coronary syndrome as defined above in a blood sample from a human, particularly human patient, in step (i) of the method according to the present invention, an algorithm or a mathematical function is applied to said expression profile (data) in step (ii) of the method of the present invention, wherein the application of said algorithm or mathematical function to said expression profile allows for the diagnosis and/or prognosis of an acute coronary syndrome.

[0148] The algorithm or mathematical function may be any algorithm or mathematical function which allows for the diagnosis and/or prognosis of an acute coronary syndrome.

[0149] As already mentioned above, the term "(clinical) condition" (biological state or health state) means a status of a subject that can be described by physical, mental or social criteria. It includes so-called "healthy" and "diseased" conditions. For the definition of "healthy" and "diseased" conditions it is referred to the international classification of diseases (ICD) of the WHO (<http://www.int.classifications/icd/en/index.html>). When an algorithm or a mathematical function obtained from a reference of one known (clinical) condition is applied to the expression profile (data) determined in a human, particularly human patient, according to preferred embodiments of the method of the present invention, it is understood that said condition is an acute coronary syndrome (i.e. diseased condition), or that said condition is no acute coronary syndrome (i.e. healthy/healthiness). When an algorithm or a mathematical function obtained from a reference of at least two known (clinical) conditions is applied to the expression profile (data) determined in a human, particularly human patient, according to other preferred embodiments of the method of the present invention, it is understood that this is possible for all (clinical) conditions that can be defined under the proviso that one known (clinical) condition is an acute coronary syndrome (i.e. diseased condition). For example, an algorithm or a mathematical function obtained from a reference of two known (clinical) conditions, which are an acute coronary syndrome and no acute coronary syndrome, may be applied to the expression profile (data) determined in a human, particularly human patient.

[0150] Preferably, the algorithm or mathematical function is obtained from a reference expression profile (data) of at least one subject, preferably of at least 2 to 40 subjects, more preferably of at least 10 to 25 subjects, and most preferably of at least 15 to 20 subjects, e.g. of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 subjects, with one known clinical condition which is an acute coronary syndrome, or which is no acute coronary syndrome (i.e. healthy/healthiness), wherein the reference expression profile is the profile of a (single) miRNA that has a nucleotide sequence that essentially corresponds (is essentially identical), preferably that corresponds (is identical), to the nucleotide sequence of the miRNA of step (i), or is the profile of a set comprising at least two miRNAs that have nucleotide sequences that essentially correspond (are essentially identical), preferably that correspond (are identical), to the nucleotide sequences of the miRNAs of step (i). It should be noted that said subject(s) is (are) human(s). Said subject(s) may also be designated as control subject(s).

[0151] For example, said algorithm or mathematical function may be obtained from a reference expression profile of at least one subject known to be not affected by an acute coronary syndrome (i.e. healthy), or known to be affected by an acute coronary syndrome (i.e. diseased), wherein the reference expression profile is the profile of a single miRNA that has a nucleotide sequence that essentially corresponds (is essentially identical), preferably that corresponds (is identical), to the nucleotide sequence of the miRNA of step (i) or is the profile of a set comprising at least two miRNAs that have nucleotide sequences that essentially correspond (are essentially identical), preferably that correspond (are identical), to the nucleotide sequences of the miRNAs of step (i).

[0152] The terms "essentially correspond(s)" or "essentially identical", as used in this aspect of the present invention, mean that the miRNA(s) of step (i) and the miRNA(s) of the reference expression profile may slightly differ in their nucleotide sequence, whereas said difference is so marginal that it may still allow for the diagnosis and/or prognosis of an acute coronary syndrome. Preferably, the nucleotide sequence(s) of the miRNA(s) of step (i) and the nucleotide sequence(s) of the miRNA(s) of the reference expression profile differ in 1 to 5, more preferably in 1 to 3, and most preferably in 1 to 2 nucleotides, i.e. in 1, 2, 3, 4, or 5 nucleotides. It is preferred that said difference resides in 1 to 5, more preferably 1 to 3, and most preferably 1 to 2 nucleotide mutations, i.e. 1, 2, 3, 4, or 5 nucleotide mutations (e.g. substitutions, additions, insertions, and/or deletions). This is caused by the fact that the miRNAs within the human species may differ. It is preferred that the miRNA(s) of step (i) and the miRNA(s) of the reference expression profile do not differ in their nucleotide sequence, i.e. are identical. It is particularly preferred that the miRNA(s) of step (i) and the miRNA(s) of the reference expression profile are derived from subject/patients of the same gender (e.g. female or male) and/or similar age/phase of life (e.g. infant, young children, juvenile, or adult).

[0153] It is particularly preferred that the algorithm or mathematical function is obtained from reference expression profiles (data) of at least two subjects, preferably of at least 3 to 40 subjects, more preferably of at least 10 to 25 subjects, and most preferably of at least 15 to 20 subjects, e.g. of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 subjects, with at least two known clinical conditions (only one known clinical condition per subject), preferably at least 2 to 5, more preferably at least 2 to 4 (e.g. at least 2, 3, 4, or 5) known clinical conditions, which are an acute coronary syndrome and any other known clinical condition(s), wherein the reference expression profiles are the profiles of a (single) miRNA that has a nucleotide sequence that essentially corresponds (is essentially identical), preferably that corresponds (is identical), to the nucleotide sequence of the miRNA of step (i) or are the profiles of a set comprising at least two miRNAs that have nucleotide sequences that essentially correspond (are essentially identical), preferably that correspond (are identical), to the nucleotide sequences of the miRNAs of step (i). It should be noted that said subject(s) is (are) human(s). Said subject(s) may also be designated as control subject(s).

[0154] Preferably, the two known clinical conditions are an acute coronary syndrome and no acute coronary syndrome.

[0155] For example, said algorithm or mathematical function may be obtained from reference expression profiles of at least two subjects, at least one subject known to suffer from an acute coronary syndrome (i.e. diseased) and at least one subject known not to suffer from an acute coronary syndrome (i.e. healthy), wherein the reference expression profile is the profile of a single miRNA that has a nucleotide sequence that essentially corresponds (is essentially identical), preferably that corresponds (is identical), to the nucleotide sequence of the miRNA of step (i) or is the profile of a set comprising at least two miRNAs that have nucleotide sequences that essentially correspond (are essentially identical), preferably that corresponds (are identical), to the nucleotide sequences of the miRNAs of step (i).

[0156] Preferably, the above-mentioned algorithm or mathematical function is obtained from reference expression profiles of the same number of (control) subjects (e.g. subjects known to be healthy or diseased). For example, the algorithm or mathematical function may be obtained from reference expression profiles of 10 subjects known to suffer from an acute coronary syndrome (positive control) and 10 subjects known not to suffer from an acute coronary syndrome (negative control). The algorithm or mathematical function may also be obtained from reference expression profiles of 20 subjects known to suffer from an acute coronary syndrome (positive control) and 20 subjects known not to suffer from an acute coronary syndrome (negative control).

[0157] It is preferred that the algorithm or mathematical function is obtained using a machine learning approach. Machine learning approaches may include but are not limited to supervised or unsupervised analysis: classification techniques (e.g. naïve Bayes, Linear Discriminant Analysis, Quadratic Discriminant Analysis Neural Nets, Tree based approaches, Support Vector Machines, Nearest Neighbour Approaches), Regression techniques (e.g. linear Regression, Multiple Regression, logistic regression, probit regression, ordinal logistic regression ordinal probit regression, Poisson Regression, negative binomial Regression, multinomial logistic Regression, truncated regression), Clustering techniques (e.g. k-means clustering, hierarchical clustering, PCA), Adaptations, extensions, and combinations of the previously mentioned approaches.

[0158] The inventors of the present invention surprisingly found that the application of a machine learning approach (e.g. t-test, AUC, support vector machine, hierarchical clustering, or k-means) leads to the obtainment of an algorithm or a mathematical function that is trained by the reference expression profile(s) (data) mentioned above and that this allows (i) a better discrimination between the at least two (e.g. 2 or 3) known clinical conditions (the at least two statistical classes) or (ii) a better decision, whether the at least one known clinical condition (the at least one statistical class) is present. In this way, the performance for diagnosing/prognosing of individuals suffering from an acute coronary syndrome can be increased (see also experimental section for details).

[0159] Preferably, the machine learning approach involves the following steps:

- (i) inputting the reference expression profile(s) of (a) subject(s) with the known clinical condition of an acute coronary syndrome and/or with any other known clinical condition(s), preferably with the known clinical condition of no acute

coronary syndrome, and

(ii) computing an algorithm or a mathematical function based on said reference expression profile(s) that is suitable to distinguish between the (likely) clinical condition of an acute coronary syndrome and any other (likely) clinical condition(s), preferably the clinical condition of no acute coronary syndrome, or to decide if the clinical condition of an acute coronary syndrome or no acute coronary syndrome is present or will likely be present in said human, particularly human patient.

[0160] It should be noted that item (ii) encompasses both that the computed algorithm or mathematical function is suitable to distinguish between the clinical condition of an acute coronary syndrome and any other clinical condition(s), preferably the clinical condition of no acute coronary syndrome, and that the computed algorithm or mathematical function is suitable to distinguish between the likely clinical condition of an acute coronary syndrome and any other likely clinical condition(s), preferably the clinical condition of no acute coronary syndrome. In this respect "likely" means that it is to be expected that the human, particularly human patient, will develop said clinical condition(s).

[0161] Thus, in a preferred embodiment, the machine learning approach involves the following steps:

(i) inputting the reference expression profile of at least one subject, preferably the reference expression profiles of at least 2 to 40 subjects, more preferably of at least 10 to 25 subjects, and most preferably of at least 15 to 20 subjects, e.g. of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 subjects, with one known clinical condition which is an acute coronary syndrome, or no acute coronary syndrome, and

(ii) computing an algorithm or a mathematical function based on said reference expression profile, preferably based on said reference expression profiles, that is suitable to decide if the clinical condition of an acute coronary syndrome, or no acute coronary syndrome is present or will likely be present in said human, particularly human patient.

[0162] Thus, in another preferred embodiment, the machine learning approach involves the following steps:

(i) inputting the reference expression profiles of at least two subjects, preferably of at least 3 to 40 subjects, more preferably of at least 10 to 25 subjects, and most preferably of at least 15 to 20 subjects, e.g. of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 subjects, with at least two known clinical conditions (only one known clinical condition per subject) which are an acute coronary syndrome and any other known clinical condition(s), preferably the known clinical condition of no acute coronary syndrome, and

(ii) computing an algorithm or a mathematical function based on said reference expression profiles that is suitable to distinguish between the (likely) clinical condition of an acute coronary syndrome, and any other (likely) clinical condition(s), preferably the clinical condition of no acute coronary syndrome.

[0163] The application of the algorithm or mathematical function as mentioned above to the expression profile of the human, particularly human patient, to be diagnosed and/or prognosed may then allow for diagnosing and/or prognosing of an acute coronary syndrome.

[0164] Considering the above, diagnosing preferably means applying the algorithm or mathematical function as mentioned above to the expression profile of a human, particularly human patient, to decide, if the at least one known clinical condition, which is an acute coronary syndrome (i.e. diseased condition), or which is no acute coronary syndrome (i.e. healthy condition), is present in said human, particularly human patient. Prognosing preferably means applying the algorithm or mathematical function as mentioned above to the expression profile of a human, particularly human patient, to decide, if the at least one known clinical condition, which is an acute coronary syndrome (i.e. diseased condition), or which is no acute coronary syndrome (i.e. healthy condition), will likely be present in said human, particularly human patient.

[0165] For example, the human, particularly human patient, may be diagnosed as not suffering from an acute coronary syndrome (i.e. being healthy), or as suffering from an acute coronary syndrome (i.e. being diseased). Further, for example, the human, particularly human patient, may be prognosed as not developing an acute coronary syndrome (i.e. staying healthy), or as developing an acute coronary syndrome (i.e. getting diseased).

[0166] Furthermore, considering the above, diagnosing preferably means applying the algorithm or mathematical function as mentioned above to the expression profile of a human, particularly human patient, to decide which of the at least two known clinical conditions, which are an acute coronary syndrome and any other known clinical condition(s), preferably the clinical condition of no acute coronary syndrome, is (are) present in said human, particularly human patient, or to distinguish between the at least two known clinical conditions, which are an acute coronary syndrome and any other known clinical condition(s), preferably the clinical condition of no acute coronary syndrome. Prognosing preferably means applying the algorithm or mathematical function as mentioned above to the expression profile of a human,

particularly human patient, to decide which of the at least two known clinical conditions, which are an acute coronary syndrome and any other known clinical condition(s), preferably the clinical condition of no acute coronary syndrome, will likely be present in said human, particularly human patient, or to distinguish between the at least two likely clinical conditions, which are an acute coronary syndrome and any other known clinical condition(s), preferably the clinical condition of no acute coronary syndrome.

[0167] For example, if the at least two known clinical conditions are an acute coronary syndrome (i.e. diseased condition) and no acute coronary syndrome (i.e. healthy condition), the human, particularly human patient, may be diagnosed as suffering from an acute coronary syndrome (i.e. being diseased), or as not suffering from an acute coronary syndrome (i.e. being healthy). If the at least two known clinical conditions are an acute coronary syndrome (i.e. diseased condition) and no acute coronary syndrome (i.e. healthy condition), the human, particularly human patient, may be prognosed as developing an acute coronary syndrome (i.e. getting diseased), or as not developing an acute coronary syndrome (i.e. staying healthy).

[0168] Diagnosing/prognosing of an acute coronary syndrome based on an algorithm or a mathematical function may take place as follows: For instance, if the algorithm or mathematical function, which is obtained from a reference expression profile of at least one subject with the known clinical condition of an acute coronary syndrome, is applied to the expression profile (data) of a human (particularly human patient), the human (particularly human patient) is classified as suffering from an acute coronary syndrome (i.e. being diseased), if the resulting score is below a specified threshold, or if the algorithm or mathematical function, which is obtained from a reference expression profile of at least one subject with the known clinical condition of no acute coronary syndrome, is applied to the expression profile (data) of a human (particularly human patient), the human (particularly human patient) is classified as not suffering from an acute coronary syndrome (i.e. being healthy), if the resulting score is above a specified threshold.

[0169] Further, if the algorithm or mathematical function, which is obtained from a reference expression profile of at least one subject with the known clinical condition of an acute coronary syndrome and from a reference expression profile of at least one subject with the known clinical condition of no acute coronary syndrome, is applied to the expression profile (data) of a human (particularly human patient), the human (particularly human patient) is classified as suffering from an acute coronary syndrome (i.e. being diseased), if the resulting score is below a specified threshold, and the human (particularly human patient) is classified as not suffering from an acute coronary syndrome (i.e. being healthy), if the resulting score is above a specified threshold.

[0170] Preferably, machine learning approaches are employed to develop/obtain algorithms or mathematical functions for diagnosing and/or prognosing of clinical conditions such as an acute coronary syndrome. Support vector machines (SVMs) are a set of related supervised learning methods which are preferably used for classification and regression. For example, given a set of training examples, each marked as belonging to one of two categories (e.g. condition of an acute coronary syndrome and no acute coronary syndrome), an SVM algorithm builds a model that predicts whether a new example (e.g. sample from a human, particularly human patient, to be tested) falls into one category or the other (e.g. condition of an acute coronary syndrome or no acute coronary syndrome). A SVM model is a representation of the training examples as points in space, mapped so that the training examples of the separate categories (e.g. condition of an acute coronary syndrome or no acute coronary syndrome) are divided by a clear gap that is as wide as possible. New examples (e.g. sample from a human, particularly human patient, to be tested) are then mapped into that same space and predicted to belong to a category based on which side of the gap they fall on (e.g. an acute coronary syndrome or no acute coronary syndrome). More formally, a support vector machine constructs a hyperplane or set of hyperplanes in a high or infinite dimensional space, which can be used for classification, regression or other tasks. A good separation is achieved by the hyperplane that has the largest distance to the nearest training data points of any class (so-called functional margin), since in general the larger the margin the lower the generalization error of the classifier.

[0171] Classifying data is a preferred task in machine learning. For example, considering some given data points each belong to one (e.g. an acute coronary syndrome or no acute coronary syndrome) of two classes (e.g. an acute coronary syndrome and no acute coronary syndrome), the goal is to decide which class a new data point (e.g. achieved from a human, particularly human patient) will be in. In the preferred case of support vector machines, a data point is viewed as a p-dimensional vector (a list of p numbers), and the question is, whether it is possible to separate such points with a p-1-dimensional hyperplane. This is called a linear classifier. There are many hyperplanes that might classify the data. One reasonable choice as the best hyperplane is the one that represents the largest separation, or margin, between the two classes (e.g. condition of an acute coronary syndrome or no acute coronary syndrome). Thus, the hyperplane should be chosen so that the distance from it to the nearest data point on each side is maximized. If such a hyperplane exists, it is known as the maximum-margin hyperplane and the linear classifier it defines is known as a maximum margin classifier.

[0172] The formalization of the support vector machine is exemplary summarised below:

For example, given are training data **D** (e.g. reference expression profile(s) of (a) subject(s) with the known clinical condition of an acute coronary syndrome and/or with any other known clinical condition(s), preferably with the known

clinical condition of no acute coronary syndrome), a set of n subject samples (e.g. subjects known to suffer from an acute coronary syndrome and/or any other known clinical condition, for example, no acute coronary syndrome) of the form

$$\mathcal{D} = \{(\mathbf{x}_i, c_i) \mid \mathbf{x}_i \in \mathbb{R}^p, c_i \in \{-1, 1\}\}_{i=1}^n$$

where the c_i is either 1 or -1, indicating the class labels (e.g. an acute coronary syndrome and/or any other known clinical condition(s), for example, no acute coronary syndrome) to which the miRNA biomarker intensities $\mathbf{x}_i$ belongs. Each $\mathbf{x}_i$ is a p -dimensional real vector (with p being the number of miRNA biomarkers). The task is know to find the maximum-margin hyperplane that divides the points having $c_i = 1$ from those having $c_i = -1$. Any hyperplane can be written as the set of points $\mathbf{x}$ satisfying

$$\mathbf{w} \cdot \mathbf{x} - b = 0,$$

where "." denotes the dot product. The vector $\mathbf{w}$ is a normal vector: it is perpendicular to the hyperplane. The parameter

$\frac{b}{\|\mathbf{w}\|}$ determines the offset of the hyperplane from the origin along the normal vector $\mathbf{w}$.

[0173] $\mathbf{w}$ and b should be chosen to maximize the margin, or distance between the parallel hyperplanes that are as far apart as possible while still separating the data. These hyperplanes can be described by the equations

$$\mathbf{w} \cdot \mathbf{x} - b = 1$$

and

$$\mathbf{w} \cdot \mathbf{x} - b = -1.$$

[0174] Note that if the training data are linearly separable, the two hyperplanes of the margin can be selected in a way that there are no points between them and then by trying to maximize their distance. For example, by using geometry,

the distance between these two hyperplanes is $\frac{2}{\|\mathbf{w}\|}$, so $\|\mathbf{w}\|$ should be minimized. To also prevent data points falling into the margin, the following constraint should be added: for each i either

$$\mathbf{w} \cdot \mathbf{x}_i - b \geq 1$$

for $\mathbf{x}_i$ of the first class (e.g. an acute coronary syndrome)
or

$$\mathbf{w} \cdot \mathbf{x}_i - b \leq -1$$

for $\mathbf{x}_i$ of the second class (no acute coronary syndrome).

[0175] This can be rewritten as:

$$c_i(\mathbf{w} \cdot \mathbf{x}_i - b) \geq 1, \quad \text{for all } 1 \leq i \leq n. \quad (1)$$

[0176] This can be put together to get the optimization problem:

Minimize (in $\mathbf{w}, b$)

$\|\mathbf{w}\|$
subject to (for any $i = 1, \dots, n$)

$$c_i(\mathbf{w} \cdot \mathbf{x}_i - b) \geq 1.$$

[0177] The optimization problem presented in the preceding section is difficult to solve because it depends on $\|\mathbf{w}\|$, the norm of $\mathbf{w}$, which involves a square root. It is, however, possible to alter the equation by substituting $\|\mathbf{w}\|$ with $\frac{1}{2}\|\mathbf{w}\|^2$ (the factor of 1/2 being used for mathematical convenience) without changing the solution (the minimum of the original and the modified equation have the same $\mathbf{w}$ and b). This is a quadratic programming (QP) optimization problem. More clearly:

Minimize (in $\mathbf{w}, b$)

$$\frac{1}{2}\|\mathbf{w}\|^2$$

subject to (for any $i = 1, \dots, n$)

$$c_i(\mathbf{w} \cdot \mathbf{x}_i - b) \geq 1.$$

[0178] The previous problem may be expressed by means of non-negative Lagrange multipliers α_i as

$$\min_{\mathbf{w}, b, \alpha} \left\{ \frac{1}{2}\|\mathbf{w}\|^2 - \sum_{i=1}^n \alpha_i [c_i(\mathbf{w} \cdot \mathbf{x}_i - b) - 1] \right\}$$

but this would lead to an incorrect result. The reason is the following: suppose that a family of hyperplanes which divide the points can be found; then all $c_i(\mathbf{w} \cdot \mathbf{x}_i - b) - 1 \geq 0$. Hence the minimum by sending all α_i to $+\infty$ could be found, and this minimum would be reached for all the members of the family, not only for the best one which can be chosen solving the original problem.

[0179] Nevertheless the previous constrained problem can be expressed as

$$\min_{\mathbf{w}, b} \max_{\alpha} \left\{ \frac{1}{2}\|\mathbf{w}\|^2 - \sum_{i=1}^n \alpha_i [c_i(\mathbf{w} \cdot \mathbf{x}_i - b) - 1] \right\}$$

looking for a saddle point. In doing so all the points which can be separated as $c_i(\mathbf{w} \cdot \mathbf{x}_i - b) - 1 > 0$ do not matter since the corresponding α_i must be set to zero.

[0180] This problem can be solved by standard quadratic programming techniques and programs. The solution can be expressed by terms of linear combination of the training vectors as

$$\mathbf{w} = \sum_{i=1}^n \alpha_i c_i \mathbf{x}_i$$

[0181] Only a few α_i will be greater than zero. The corresponding $\mathbf{x}_i$ are exactly the *support vectors*, which lie on the margin and satisfy $c_i (\mathbf{w} \cdot \mathbf{x}_i - b) = 1$. From this it can be derived that the support vectors also satisfy

$$\mathbf{w} \cdot \mathbf{x}_i - b = 1/c_i = c_i \iff b = \mathbf{w} \cdot \mathbf{x}_i - c_i$$

which allows one to define the offset b . In practice, it is more robust to average over all N_{SV} support vectors:

$$b = \frac{1}{N_{SV}} \sum_{i=1}^{N_{SV}} (\mathbf{w} \cdot \mathbf{x}_i - c_i)$$

[0182] Writing the classification rule in its unconstrained dual form reveals that the maximum margin hyperplane and therefore the classification task is only a function of the *support vectors*, the training data that lie on the margin.

[0183] Using the fact, that $\|\mathbf{w}\|^2 = \mathbf{w} \cdot \mathbf{w}$ and substituting $\mathbf{w} = \sum_{i=0}^n \alpha_i c_i \mathbf{x}_i$ it can show shown that the dual of the SVM reduces to the following optimization problem:

Maximize (in α_i)

$$\tilde{L}(\alpha) = \sum_{i=1}^n \alpha_i - \frac{1}{2} \sum_{i,j} \alpha_i \alpha_j c_i c_j \mathbf{x}_i^T \mathbf{x}_j = \sum_{i=1}^n \alpha_i - \frac{1}{2} \sum_{i,j} \alpha_i \alpha_j c_i c_j k(\mathbf{x}_i, \mathbf{x}_j)$$

subject to (for any $i = 1, \dots, n$)

$$\alpha_i \geq 0,$$

and to the constraint from the minimization in b

$$\sum_{i=1}^n \alpha_i c_i = 0.$$

[0184] Here the kernel is defined by $k(\mathbf{x}_i, \mathbf{x}_j) = \mathbf{x}_i \cdot \mathbf{x}_j$.

[0185] The α terms constitute a dual representation for the weight vector in terms of the training set:

$$\mathbf{w} = \sum_i \alpha_i c_i \mathbf{x}_i.$$

[0186] For simplicity reasons, sometimes it is required that the hyperplane passes through the origin of the coordinate system. Such hyperplanes are called *unbiased*, whereas general hyperplanes not necessarily passing through the origin are called *biased*. An unbiased hyperplane can be enforced by setting $b = 0$ in the primal optimization problem. The corresponding dual is identical to the dual given above without the equality constraint

$$\sum_{i=1}^n \alpha_i c_i = 0.$$

[0187] Transductive support vector machines extend SVMs in that they could also treat partially labeled data in semi-supervised learning. Here, in addition to the training set $\mathcal{D}$, the learner is also given a set

$$\mathcal{D}^* = \{\mathbf{x}_i^* | \mathbf{x}_i^* \in \mathbb{R}^p\}_{i=1}^k$$

of test examples to be classified. Formally, a transductive support vector machine is defined by the following primal optimization problem:

Minimize (in $\mathbf{w}$, b , $\mathbf{c}^*$)

$$\frac{1}{2} \|\mathbf{w}\|^2$$

subject to (for any $i = 1, \dots, n$ and any $j = 1, \dots, k$)

$$c_i (\mathbf{w} \cdot \mathbf{x}_i - b) \geq 1,$$

$$c_j^* (\mathbf{w} \cdot \mathbf{x}_j^* - b) \geq 1,$$

and

$$c_j^* \in \{-1, 1\}.$$

[0188] Transductive support vector machines were introduced by Vladimir Vapnik in 1998.

[0189] SVMs belong to a family of generalized linear classifiers. They can also be considered a special case of Tikhonov regularization. A special property is that they simultaneously minimize the empirical *classification error* and maximize the *geometric margin*; hence they are also known as maximum margin classifiers.

[0190] In 1995, Corinna Cortes and Vladimir Vapnik suggested a modified maximum margin idea that allows for mislabeled examples. If there exists no hyperplane that can split the "yes" and "no" examples, the *Soft Margin* method will choose a hyperplane that splits the examples as cleanly as possible, while still maximizing the distance to the nearest cleanly split examples. The method introduces slack variables, ξ_i , which measure the degree of misclassification of the datum x_i

$$c_i (\mathbf{w} \cdot \mathbf{x}_i - b) \geq 1 - \xi_i \quad 1 \leq i \leq n. \quad (2)$$

[0191] The objective function is then increased by a function which penalizes non-zero ξ_i , and the optimization becomes a trade off between a large margin, and a small error penalty. If the penalty function is linear, the optimization problem becomes:

$$\min_{\mathbf{w}, \xi} \left\{ \frac{1}{2} \|\mathbf{w}\|^2 + C \sum_{i=1}^n \xi_i \right\}$$

subject to (for any $i = 1, \dots, n$)

$$c_i(\mathbf{w} \cdot \mathbf{x}_i - b) \geq 1 - \xi_i, \quad \xi_i \geq 0.$$

[0192] This constraint in (2) along with the objective of minimizing $\|\mathbf{w}\|$ can be solved using Lagrange multipliers as done above. One has then to solve the following problem

$$\min_{\mathbf{w}, \xi} \max_{\alpha, \beta} \left\{ \frac{1}{2} \|\mathbf{w}\|^2 + C \sum_{i=1}^n \xi_i - \sum_{i=1}^n \alpha_i [c_i(\mathbf{w} \cdot \mathbf{x}_i - b) - 1 + \xi_i] - \sum_{i=1}^n \beta_i \xi_i \right\}$$

with $\alpha_i, \beta_i \geq 0$.

[0193] The key advantage of a linear penalty function is that the slack variables vanish from the dual problem, with the constant C appearing only as an additional constraint on the Lagrange multipliers. For the above formulation and its huge impact in practice, Cortes and Vapnik received the 2008 ACM Paris Kanellakis Award. Non-linear penalty functions have been used, particularly to reduce the effect of outliers on the classifier, but unless care is taken, the problem becomes non-convex, and thus it is considerably more difficult to find a global solution.

[0194] The original optimal hyperplane algorithm proposed by Vladimir Vapnik in 1963 was a linear classifier. However, in 1992, Bernhard Boser, Isabelle Guyon and Vapnik suggested a way to create non-linear classifiers by applying the kernel trick (originally proposed by Aizerman et al.^[4]) to maximum-margin hyperplanes. The resulting algorithm is formally similar, except that every dot product is replaced by a non-linear kernel function. This allows the algorithm to fit the maximum-margin hyperplane in a transformed feature space. The transformation may be non-linear and the transformed space high dimensional; thus though the classifier is a hyperplane in the high-dimensional feature space, it may be non-linear in the original input space.

[0195] If the kernel used is a Gaussian radial basis function, the corresponding feature space is a Hilbert space of infinite dimension. Maximum margin classifiers are well regularized, so the infinite dimension does not spoil the results. Some common kernels include,

- Polynomial (homogeneous): $k(\mathbf{x}_i, \mathbf{x}_j) = (\mathbf{x}_i \cdot \mathbf{x}_j)^d$
- Polynomial (inhomogeneous): $k(\mathbf{x}_i, \mathbf{x}_j) = (\mathbf{x}_i \cdot \mathbf{x}_j + 1)^d$
- Radial Basis Function: $k(\mathbf{x}_i, \mathbf{x}_j) = \exp(-\gamma \|\mathbf{x}_i - \mathbf{x}_j\|^2)$, for $\gamma > 0$
- Gaussian Radial basis function: $k(\mathbf{x}_i, \mathbf{x}_j) = \exp\left(-\frac{\|\mathbf{x}_i - \mathbf{x}_j\|^2}{2\sigma^2}\right)$
- Hyperbolic tangent: $k(\mathbf{x}_i, \mathbf{x}_j) = \tanh(\kappa \mathbf{x}_i \cdot \mathbf{x}_j + c)$, for some (not every) $\kappa > 0$ and $c < 0$

[0196] The kernel is related to the transform $\varphi(\mathbf{x}_i)$ by the equation $k(\mathbf{x}_i, \mathbf{x}_j) = \varphi(\mathbf{x}_i) \cdot \varphi(\mathbf{x}_j)$. The value w is also in the transformed space, with $\mathbf{w} = \sum_i \alpha_i \varphi(\mathbf{x}_i)$. Dot products with w for classification can again be computed by the kernel trick, i.e. $\mathbf{w} \cdot \varphi(\mathbf{x}) = \sum_i \alpha_i k(\mathbf{x}_i, \mathbf{x})$. However, there does not in general exist a value w' such that $\mathbf{w} \cdot \varphi(\mathbf{x}) = k(\mathbf{w}', \mathbf{x})$.

[0197] After the $\mathbf{w}$ and b are determined employing the above-mentioned methods these can be used for classifying new datasets (e.g. a expression profile of a patient with p miRNA biomarkers and corresponding $\mathbf{x}_i$ intensity values).

[0198] As described above, the method of the present invention may also comprise the following second step with both afore-mentioned alternatives:

- (ii) comparing said expression profile to a reference, wherein the comparison of said expression profile to said reference allows for the diagnosis and/or prognosis of an acute coronary syndrome and applying an algorithm or a mathematical function to said expression profile, wherein the application of said algorithm or mathematical function

to said expression profile allows for the diagnosis and/or prognosis of an acute coronary syndrome.

[0199] Thus, subsequent to the determination of an expression profile (data) of a (single) miRNA representative for an acute coronary syndrome as defined above, or of a set comprising at least two miRNAs representative for an acute coronary syndrome as defined above in a blood sample from a human, particularly human patient, in step (i) of the method according to the present invention, said expression profile (data) is compared to a reference, as defined/described above, in step (ii) of the method according to the present invention, wherein the comparison of said expression profile (data) to said reference allows for the diagnosis and/or prognosis of an acute coronary syndrome, and an algorithm or a mathematical function is applied to said expression profile (data), as defined/described above, in step (ii) of the method of the present invention, wherein the application of said algorithm or mathematical function to said expression profile allows for the diagnosis and/or prognosis of an acute coronary syndrome.

[0200] As mentioned above, the measured miRNA expression profiles may be classified using machine learning approaches in order to compute accuracy, specificity, and sensitivity for the diagnosis and/or prognosis of an acute coronary syndrome (see experimental section for more details). Examples of miRNA sets (signatures) that performed best for the diagnosis of an acute coronary syndrome according to their accuracy, specificity, and sensitivity are miRNAs having SEQ ID NO: 1 and 2 (see Figure 13), miRNAs having SEQ ID NO: 1 to 4 (see Figure 14), SEQ ID NO: 1 to 6 (see Figure 15), SEQ ID NO: 1 to 8 (see Figure 16), SEQ ID NO: 1 to 10 (see Figure 17), SEQ ID NO: 1 to 50 (see Figure 18), SEQ ID NO: 1 to 80 (see Figure 19), or SEQ ID NO: 1 to 100 (see Figure 20). Further miRNA sets (signatures) that performed best for the diagnosis of an acute coronary syndrome according to their accuracy, specificity, and sensitivity are summarized in Figures 28 and 30.

[0201] Preferably, the reference and optionally the expression profile of the miRNA(s) representative for an acute coronary syndrome is (are) stored in a database.

[0202] The above-mentioned method is for diagnosing an acute coronary syndrome in a human, particularly human patient. Preferably, the diagnosis comprises (i) determining the occurrence/presence of an acute coronary syndrome, (ii) monitoring the course of an acute coronary syndrome, (iii) staging of an acute coronary syndrome, (iv) measuring the response of an individual, particularly human patient, with an acute coronary syndrome to therapeutic intervention, and/or (v) segmentation of individuals, particularly human patients, suffering from an acute coronary syndrome.

[0203] The above-mentioned method is also for prognosis of an acute coronary syndrome in a human, particularly human patient. Preferably, the prognosis comprises (i) identifying an individual, particularly human patient, who has a risk to develop an acute coronary syndrome, (ii) predicting/estimating the occurrence, preferably the severity of occurrence, of an acute coronary syndrome, and/or (iii) predicting the response of an individual, particularly human patient with an acute coronary syndrome to therapeutic intervention.

[0204] In a third aspect, the present invention provides means for diagnosing and/or prognosing of an acute coronary syndrome comprising a polynucleotide (probe) or a set comprising, essentially consisting of, or consisting of at least two polynucleotides (probes) according to the first aspect of the present invention, e.g. (i) a polynucleotide for detecting a miRNA or a set comprising, essentially consisting of, or consisting of at least two polynucleotides for detecting a set comprising, essentially consisting of, or consisting of at least two miRNAs, wherein the nucleotide sequence of said miRNA or nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, or particularly (ii) a polynucleotide for detecting a miRNA or a set comprising, essentially consisting of, or consisting of at least 2, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153, polynucleotides for detecting a set comprising, essentially consisting of, or consisting of at least 2, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153, miRNAs, wherein the nucleotide sequence of said miRNA or nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153. It is preferred that said polynucleotide set, in (ii) above, comprises at least one further polynucleotide (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 polynucleotide(s)) for detecting the above-mentioned miRNA set comprising at least one further miRNA (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31,

32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 miRNA(s)), wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241.

[0205] Preferably, the means for diagnosing and/or prognosing of an acute coronary syndrome comprises, essentially consists of, or consists of a solid support, substrate, surface, platform or matrix comprising a polynucleotide (probe) or a set comprising, essentially consisting of, or consisting of at least two polynucleotides (probes) according to the first aspect of the present invention, e.g. (i) a solid support, substrate, surface, platform or matrix comprising a polynucleotide for detecting a miRNA or a set comprising, essentially consisting of, or consisting of at least two polynucleotides for detecting a set comprising, essentially consisting of, or consisting of at least two miRNAs, wherein the nucleotide sequence of said miRNA or nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, or particularly (ii) a solid support, substrate, surface, platform or matrix comprising a polynucleotide for detecting a miRNA or a set comprising, essentially consisting of, or consisting of at least 2, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153, polynucleotides for detecting a set comprising, essentially consisting of, or consisting of at least 2, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153, miRNAs, wherein the nucleotide sequence of said miRNA or nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153. It is preferred that said polynucleotide set, in (ii) above, comprises at least one further polynucleotide (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 polynucleotide(s)) for detecting the above-mentioned miRNA set comprising at least one further miRNA (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 miRNA(s)), wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241. Preferably, the above-mentioned polynucleotide(s) is (are) attached to or immobilized on a solid support, substrate, surface, platform or matrix. It is possible to include appropriate controls for non-specific hybridization on the solid support, substrate, surface, platform or matrix.

[0206] It is particularly preferred that said means for diagnosing and/or prognosing of an acute coronary syndrome comprises, essentially consists of, or consists of a microarray/biochip comprising a polynucleotide (probe) or a set comprising, essentially consisting of, or consisting of at least two polynucleotides (probes) according to the first aspect of the present invention, e.g. (i) a microarray/biochip comprising a polynucleotide for detecting a miRNA or a set comprising, essentially consisting of, or consisting of at least two polynucleotides for detecting a set comprising, essentially consisting of, or consisting of at least two miRNAs, wherein the nucleotide sequence of said miRNA or nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, or particularly (ii) a microarray/biochip comprising a polynucleotide for detecting a miRNA or a set comprising, essentially consisting of, or consisting of at least 2, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153, polynucleotides for detecting a set comprising, essentially consisting of, or consisting of at least 2, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153, miRNAs, wherein the nucleotide sequence of said miRNA or nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153. It is preferred that said polynucleotide set, in (ii) above,

comprises at least one further polynucleotide (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 polynucleotide(s)) for detecting the above-mentioned miRNA set comprising at least one further miRNA (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 miRNA(s)), wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241. Preferably, the above-mentioned polynucleotide(s) is (are) attached to or immobilized on the microarray/biochip. It is possible to include appropriate controls for non-specific hybridization on the microarray/biochip.

[0207] It is further particularly preferred that said means for diagnosing and/or prognosing of an acute coronary syndrome comprise, essentially consists of, or consists of a set comprising at least two polynucleotides for detecting a set comprising at least two miRNAs, wherein the nucleotide sequences of said miRNAs are selected from one or more sets listed in Figure 28 and/or Figure 30. Preferably, said polynucleotides are attached to or immobilized on a solid support, substrate, surface, platform or matrix, more preferably microarray/biochip.

[0208] The polynucleotide(s) (probe(s)) may also be comprised as polynucleotide fragments, polynucleotide variants, or polynucleotide fragment variants in the means for diagnosing and/or prognosing of an acute coronary syndrome. For example, polynucleotide fragments, polynucleotide variants, or polynucleotide fragment variants may be comprised in the solid support, substrate, surface, platform or matrix, preferably microarray/biochip. Said polynucleotide fragments, polynucleotide variants, or polynucleotide fragment variants may be attached or linked to the solid support, substrate, surface, platform or matrix, preferably microarray/biochip. As to the definition of said polynucleotide fragments, polynucleotide variants, or polynucleotide fragment variants and as to the preferred polynucleotide (probe) or sets of polynucleotides (probes), it is referred to the first aspect of the present invention.

[0209] The terms "biochip" or "microarray", as used herein, refer to a solid phase comprising an attached or immobilized polynucleotide described herein as probe or a set (plurality) of polynucleotides described herein attached or immobilized as probes. The polynucleotide probes may be capable of hybridizing to a target sequence, such as a complementary miRNA or miRNA* sequence, under stringent hybridization conditions. The polynucleotide probes may be attached or immobilized at spatially defined locations on the solid phase. One or more than one nucleotide (probe) per target sequence may be used. The polynucleotide probes may either be synthesized first, with subsequent attachment to the biochip, or may be directly synthesized on the biochip. The solid phase may be a material that may be modified to contain discrete individual sites appropriate for the attachment or association of the polynucleotide probes and is amenable to at least one detection method. Representative examples of solid phase materials include glass and modified or functionalized glass, plastics (including acrylics, polystyrene and copolymers of styrene and other materials, polypropylene, polyethylene, polybutylene, polyurethanes, Teflon, etc.), polysaccharides, nylon or nitrocellulose, resins, silica or silica-based materials including silicon and modified silicon, carbon, metals, inorganic glasses and plastics. The solid phase may allow optical detection without appreciably fluorescing. The solid phase may be planar, although other configurations of solid phase may be used as well. For example, polynucleotide probes may be placed on the inside surface of a tube, for flow-through sample analysis to minimize sample volume. Similarly, the solid phase may be flexible, such as flexible foam, including closed cell foams made of particular plastics. The solid phase of the biochip and the probe may be modified with chemical functional groups for subsequent attachment of the two. For example, the biochip may be modified with a chemical functional group including, but not limited to, amino groups, carboxyl groups, oxo groups or thiol groups. Using these functional groups, the probes may be attached using functional groups on the probes either directly or indirectly using a linker. The polynucleotide probes may be attached to the solid support by either the 5' terminus, 3' terminus, or via an internal nucleotide. The polynucleotide probe may also be attached to the solid support non-covalently. For example, biotinylated polynucleotides can be made, which may bind to surfaces covalently coated with streptavidin, resulting in attachment. Alternatively, polynucleotide probes may be synthesized on the surface using techniques such as photopolymerization and photolithography. In the context of the present invention, the terms "biochip" and "microarray" are interchangeable used.

[0210] The terms "attached" or "immobilized", as used herein, refer to the binding between the polynucleotide and the solid support/phase and may mean that the binding between the polynucleotide probe and the solid support is sufficient to be stable under conditions of binding, washing, analysis and removal. The binding may be covalent or non-covalent. Covalent bonds may be formed directly between the polynucleotide and the solid support or may be formed by a cross linker or by inclusion of specific reactive groups on either the solid support or the polynucleotide, or both. Non-covalent binding may be electrostatic, hydrophilic and hydrophobic interactions or combinations thereof. Immobilization or attachment may also involve a combination of covalent and non-covalent interactions.

[0211] In a fourth aspect, the present invention provides a kit for diagnosing and/or prognosing of an acute coronary syndrome comprising

(i) means for determining an expression profile of a miRNA or a set comprising, essentially consisting of, or consisting of at least 2 miRNAs, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, or 283 miRNAs, representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, a fragment thereof, and a sequence having at least 80% sequence identity thereto; and

(ii) at least one reference and/or algorithm or mathematical function, preferably comprised on at least one data carrier.

[0212] In a preferred embodiment, the present invention provides a kit for diagnosing and/or prognosing of an acute coronary syndrome comprising

(i) means for determining an expression profile of a miRNA or a set comprising, essentially consisting of, or consisting of at least 2 miRNAs, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, or 153 miRNAs, representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, a fragment thereof, and a sequence having at least 80% sequence identity thereto; and

(ii) at least one reference and/or algorithm or mathematical function, preferably comprised on at least one data carrier.

[0213] Preferably, the above-mentioned set of miRNAs comprises at least one further miRNA (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 miRNA(s)), wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, a fragment thereof, and a sequence having at least 80% sequence identity thereto.

[0214] The nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs may also be selected from the group consisting of SEQ ID NO: 242 to SEQ ID NO: 283, a fragment thereof, and a sequence having at least 80% sequence identity thereto.

[0215] In another preferred embodiment, the present invention provides a kit for diagnosing and/or prognosing of an acute coronary syndrome comprising

(i) means for determining an expression profile of a miRNA or a set comprising, essentially consisting of, or consisting of at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA is selected from the list of Figure 29, or the nucleotide sequences of said miRNAs are selected from one or more sets listed in Figure 28 and/or Figure 30; and

(ii) at least one reference and/or algorithm or mathematical function, preferably comprised on at least one data carrier.

[0216] For example, the nucleotide sequences of said miRNAs may be selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more sets listed in Figure 28 and/or Figure 30.

[0217] Said means may comprise (i) polynucleotides according to the first aspect of the present invention, (ii) means according to the third aspect of the present invention, (iii) primers suitable to perform reverse transcriptase reaction and/or real time polymerase chain reaction such as quantitative polymerase chain reaction.

[0218] It is preferred that said kit comprises

(ia) a polynucleotide for detecting a miRNA or a set comprising, essentially consisting of, or consisting of at least two polynucleotides according to the first aspect of the present invention, and
 (ib) a solid support, substrate, surface, platform or matrix onto which the polynucleotide or the set comprising at least two polynucleotides according to the first aspect of the present invention may be attached or immobilized, and
 (ic) optionally at least one of the means selected from the group consisting of: at least one human blood sample, e.g. serum, plasma, or blood cells, or at least one sample of total RNA extracted from a human blood sample, means to extract RNA from a blood sample, means for input/injection of a blood sample, positive controls for hybridization, means for holding the solid support, substrate, platform or matrix, e.g. after immobilization of the polynucleotide probe(s), means for labelling the isolated miRNA (e.g. NTP/biotin-NTP), means for hybridization, means to carry out enzymatic reactions (e.g. exonuclease I and/or Klenow enzyme) means for washing steps, means for detecting the hybridization signal, and mean for analysing the detected hybridization signal,

e.g. for determining an expression profile of a miRNA or a set comprising, essentially consisting of, or consisting of at least 2 miRNAs, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, or 153 miRNAs, representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, a fragment thereof, and a sequence having at least 80% sequence identity thereto, and more preferably for determining an expression profile of at least one further miRNA (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 miRNA(s)) comprised in said miRNA set, wherein the nucleotide sequence of the at least one further miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, a fragment thereof, and a sequence having at least 80% sequence identity thereto.

[0219] It is further preferred that said kit comprises means according to the third aspect of the present invention, e.g. means for diagnosing and/or prognosis of an acute coronary syndrome comprising a polynucleotide or a set comprising at least two polynucleotides according to the first aspect of the present invention. It is also preferred that said kit comprises means for diagnosing and/or prognosis of an acute coronary syndrome comprising a biochip which comprises a polynucleotide or a set comprising at least two polynucleotides according to the first aspect of the present invention.

[0220] It is particularly preferred that said kit comprises

(ia) a solid support, substrate, surface, platform or matrix according to the third aspect of the present invention comprising a polynucleotide or a set comprising, essentially consisting of, or consisting of at least two polynucleotides according to the first aspect of the present invention, and
 (ib) optionally at least one of the means selected from the group consisting of: at least one human blood sample, e.g. serum, plasma, or blood cells, or at least one sample of total RNA extracted from a human blood sample, means to extract RNA from a blood sample, means for input/injection of a blood sample, positive controls for the hybridization experiment, means for holding the solid support, substrate, platform or matrix comprising the polynucleotide probe(s), means for labelling the isolated miRNA (e.g. NTP/biotin-NTP), means for hybridization, means to carry out enzymatic reactions (e.g. exonuclease I and/or Klenow enzyme) means for washing steps, means for detecting the hybridization signal, and mean for analysing the detected hybridization signal,

e.g. for determining an expression profile of a miRNA or a set comprising, essentially consisting of, or consisting of at least 2 miRNAs, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, or 153 miRNAs, representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, a fragment thereof, and a sequence having at least 80% sequence identity thereto, and more preferably for determining an expression profile of at least one further miRNA (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43,

44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 miRNA(s)) comprised in said miRNA set, wherein the nucleotide sequence of the at least one further miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, a fragment thereof, and a sequence having at least 80% sequence identity thereto.

[0221] It is mostly preferred that said kit comprises

(ia) a microarray/biochip according to the third aspect of the present invention comprising a polynucleotide or a set comprising, essentially consisting of, or consisting of at least two polynucleotides according to the first aspect of the present invention, and

(ib) optionally at least one of the means selected from the group consisting of: at least one human blood sample, e.g. serum, plasma, or blood cells, or at least one sample of total RNA extracted from a human blood sample, means to extract RNA from a blood sample, means for input/injection of a blood sample, positive controls for the hybridization experiment, means for holding the microarray/biochip comprising the polynucleotide probe(s), means for labelling the isolated miRNA (e.g. NTP/biotin-NTP), means for hybridization, means to carry out enzymatic reactions (e.g. exonuclease I and/or Klenow enzyme) means for washing steps, means for detecting the hybridization signal, and mean for analysing the detected hybridization signal,

e.g. for determining an expression profile of a miRNA or a set comprising, essentially consisting of, or consisting of at least 2 miRNAs, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, or 153 miRNAs, representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, a fragment thereof, and a sequence having at least 80% sequence identity thereto, and more preferably for determining an expression profile of at least one further miRNA (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 miRNA(s)) comprised in said miRNA set, wherein the nucleotide sequence of the at least one further miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, a fragment thereof, and a sequence having at least 80% sequence identity thereto.

[0222] Preferably, the above-mentioned polynucleotide(s) is (are) attached to or immobilized on a solid support, substrate, surface, platform or matrix, more preferably microarray/biochip.

[0223] It is particularly preferred that said kit comprises

(ia) a miRNA-specific primer for reverse transcription of miRNA in miRNA-specific cDNA for a single miRNA or at least two miRNA-specific primers for reverse transcription of miRNAs in miRNA-specific cDNAs for at least 2, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153 miRNAs comprised in a set of miRNAs, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, and more preferably at least one further miRNA-specific primer for reverse transcription of miRNA in miRNA-specific cDNA for at least one further miRNA (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 miRNA(s)) comprised in the above-mentioned miRNA set, wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, and

(ib) preferably, a primer set comprising a forward primer which is specific for the cDNA obtained from the miRNA and an universal reverse primer for amplifying the cDNA obtained from the miRNA via real time polymerase chain reaction (RT-PCR) such as real time quantitative polymerase chain reaction (RT qPCR) for the single cDNA obtained from the miRNA or at least two primer sets comprising a forward primer which is specific for the single cDNA obtained from the miRNA and an universal reverse primer for amplifying the cDNA obtained from the miRNA via real time

polymerase chain reaction (RT-PCR) such as real time quantitative polymerase chain reaction (RT qPCR) for at least 2, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153 cDNAs obtained from miRNAs comprised in the set of miRNAs, wherein said cDNA is complementary to the nucleotide sequence of the miRNA or said cDNAs are complementary to the nucleotide sequences of miRNAs selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, and more preferably at least one further primer set comprising a forward primer which is specific for the cDNA obtained from the miRNA and an universal reverse primer for amplifying the cDNA obtained from the miRNA via real time polymerase chain reaction (RT-PCR) such as real time quantitative polymerase chain reaction (RT qPCR) for at least one further cDNA obtained from the miRNA (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 cDNA(s) obtained from the miRNA(s)) comprised in the above-mentioned set, wherein said cDNA is complementary to the nucleotide sequence of the miRNA selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, and

(ic) optionally at least one of the means selected from the group consisting of: at least one human blood sample, e.g. serum, plasma, or blood cells, or at least one sample of total RNA extracted from a human blood sample, means to extract RNA from a blood sample, additional means to carry out the reverse transcriptase reaction (miRNA in cDNA) (e.g. reverse transcriptase (RT) enzyme, buffers, dNTPs, RNase inhibitor), additional means to carry out real time polymerase chain reaction (RT-PCR) such as real time quantitative PCR (RT qPCR) (e.g. enzymes, buffers, water), means for labelling (e.g. fluorescent label and/or quencher), positive controls for reverse transcriptase reaction and real time PCR, and means for analysing the real time polymerase chain reaction (RT-PCR) result,

e.g. for determining an expression profile of a miRNA or a set comprising, essentially consisting of, or consisting of at least 2 miRNAs, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153 miRNAs, representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, a fragment thereof, and a sequence having at least 80% sequence identity thereto, and more preferably for determining an expression profile of at least one further miRNA comprised in said miRNA set (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 miRNA(s)), wherein the nucleotide sequence of the at least one further miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, a fragment thereof, and a sequence having at least 80% sequence identity thereto.

[0224] The primer as defined in (i) above may also be an oligo-dT primer, e.g. if the miRNA comprises a polyA tail (e.g. as result of a miRNA elongation, for example, subsequent to RNA extraction) or a miRNA specific looped RT primer.

[0225] It is further preferred that said kit comprises means for conducting next generation sequencing in order to determine an expression profile of a miRNA or a set comprising, essentially consisting of, or consisting of at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, particularly of SEQ ID NO: 1 to SEQ ID NO: 153, a fragment thereof, and a sequence having at least 80% sequence identity thereto. Preferably, said kit further comprises at least one human blood sample, e.g. blood serum, blood plasma, or blood cells. It is also preferred that said kit comprises at least one sample of total RNA extracted from a blood sample of a human, particularly human patient.

[0226] As to the definition of the miRNA fragment, miRNA variant, or miRNA fragment variant mentioned above and as to the preferred miRNA or sets of miRNAs detected, it is referred to the second aspect of the present invention.

[0227] As already mentioned above, the kit may comprise, as a first alternative,

(ii) at least one reference.

[0228] It is preferred that said reference is comprised on at least one data carrier.

[0229] The at least one reference may allow for the diagnosis and/or prognosis of an acute coronary syndrome. The at least one reference may be any reference which allows for the diagnosis and/or prognosis of an acute coronary syndrome, e.g. indicated reference data or value(s). As mentioned above (second aspect of the present invention, first alternative of step (ii)), said reference may be, in the simplest case/form, a reference control, for example, the indication of reference expression level(s) of the same miRNA(s) tested in the human, particularly human patient, to be diagnosed, but determined in the blood of a human known to be healthy, i.e. not suffering from an acute coronary syndrome, and/or the indication of reference expression level(s) of the same miRNA(s) tested in the human, particularly human patient, to be diagnosed, but determined in a human known to suffer from an acute coronary syndrome (e.g. myocardial infarction such as non-ST segment elevation myocardial infarction or ST segment elevation myocardial infarction, or Unstable angina (UA), or the like).

[0230] It is particularly preferred that said reference is a reference expression profile (data) of at least one subject, preferably the reference is an average expression profile (data) of at least 2 to 40 subjects, more preferably at least 10 to 25 subjects, and most preferably at least 15 to 20 subjects, with one known clinical condition which is an acute coronary syndrome, or which is no acute coronary syndrome (i.e. healthy/healthiness), wherein the reference expression profile is the profile of a (single) miRNA that has a nucleotide sequence that essentially corresponds (is essentially identical), preferably that corresponds (is identical), to the nucleotide sequence of the miRNA which expression profile is determinable by the means of (i) or is the profile of a set comprising at least two miRNAs that have nucleotide sequences that essentially correspond (are essentially identical), preferably that correspond (are identical), to the nucleotide sequences of the miRNAs which expression profile is determinable by the means of (i). It should be noted that said subject(s) is (are) human(s). Said subject(s) may also be designated as control subject(s).

[0231] The term "essentially corresponds (essentially identical)", as used in this aspect of the present invention, means that the miRNA(s) which expression profile is determinable by the means of (i) and the miRNA(s) of the reference expression profile may slightly differ in their nucleotide sequence, whereas said difference is so marginal that it may still allow for the diagnosis and/or prognosis of an acute coronary syndrome. Preferably, the nucleotide sequence(s) of the miRNA(s) which expression profile is determinable by the means of (i) and the nucleotide sequence(s) of the miRNA(s) of the reference expression profile differ in 1 to 5, more preferably in 1 to 3, and most preferably in 1 to 2 nucleotides, i.e. in 1, 2, 3, 4, or 5 nucleotides. It is preferred that said difference resides in 1 to 5, more preferably 1 to 3, and most preferably 1 to 2 nucleotide mutations, i.e. 1, 2, 3, 4, or 5 nucleotide mutations (e.g. substitutions, additions, insertions, and/or deletions).

[0232] The at least one reference, particularly the above-mentioned reference control (reference information) or the above-mentioned reference expression profile (data) may be comprised in the kit in form of or on an information leaflet/information sheet (e.g. for comparing tested single reference miRNA biomarkers/data with the expression profile data of a human, particularly human patient, to be diagnosed and/or prognosed), or may be comprised, e.g. saved, on a or at least one data carrier (e.g. for comparing tested sets of miRNA biomarkers/data with the expression profile data of a human, particularly human patient, to be diagnosed and/or prognosed). Said data carrier may be an electronically data carrier such as a floppy disk, a compact disk (CD), or a digital versatile disk (DVD).

[0233] Preferably, it is indicated, e.g. on the information leaflet/information sheet or data carrier, in which type of blood sample (e.g. whole blood or blood fraction such as serum or plasma) and/or from which (control) subject(s) (e.g. gender and/or age or stage of life), the (average) reference expression profile (data), which is (are) provided with the kit, has (have) been determined. It is preferred that the expression profile (data) of the human, particularly human patient, will be determined in the same type of blood sample and/or will be obtained from a human, particularly human patient, of the same gender and/or similar age or stage of life.

[0234] Said reference may also be an algorithm or mathematical function, e.g. obtained using a machine learning approach. With said algorithm or mathematical function, the algorithm or mathematical function mentioned in a preferred embodiment of the first alternative of step (ii) of the method of the second aspect is particularly meant (see above). Said reference may further be a computer program, wherein the algorithm or mathematical function is comprised. Preferably, said algorithm or mathematical function is trained by reference data (e.g. miRNA reference expression data/profiles from humans known to be healthy and/or miRNA reference expression data/profiles of humans known to suffer from an acute coronary syndrome) to discriminate between the two or more statistical classes (the two or more clinical conditions, e.g. the two conditions healthy or suffering from an acute coronary syndrome). Preferably, the algorithm or mathematical function is comprised, e.g. saved, on a data carrier comprised in the kit or the computer program, wherein the algorithm or mathematical function is comprised, is comprised, e.g. saved, on a data carrier comprised in the kit. The data carrier can be a data carrier as described above.

[0235] The kit may alternatively comprise an access code, preferably comprised on a data carrier, which allows the access to a database, e.g. an internet database, a centralized, or a decentralized database, where (i) the reference, preferably the (average) reference expression profile (data), is comprised, or (ii) where a computer program comprising the reference, preferably the (average) reference expression profile (data), can be downloaded.

[0236] More than one reference may be comprised in the kit, e.g. 2, 3, 4, 5, or more references. Thus, for example, reference (expression profile) data/reference information may be comprised as or on an information leaflet/information sheet (e.g. for comparing tested single reference miRNA biomarkers/data with the expression profile data of a human, particularly human patient, to be diagnosed) and/or may be comprised in a computer program as mentioned above (e.g. for comparing tested sets of miRNA biomarkers/data with the expression profile data of a human, particularly human patient, to be diagnosed). Further, for example, reference (expression profile) data/reference information may be comprised as or on an information leaflet/information sheet and/or may be comprised on a data carrier as described above. Furthermore, the kit may comprise more than one algorithm or mathematical function, e.g. two algorithms or mathematical functions, e.g. one trained to discriminate between a healthy condition and an acute coronary syndrome and one trained to discriminate between a myocardial infarction and an Unstable angina (UA), e.g. as part of a computer program.

[0237] As already mentioned above, the kit may comprise, as a second alternative,

(ii) at least one algorithm or mathematical function.

[0238] It is preferred that said algorithm or mathematical function is comprised on at least one data carrier.

[0239] With said algorithm or mathematical function, the algorithm or mathematical function mentioned in the second alternative of step (ii) of the method of the second aspect is particularly meant. The at least one algorithm or mathematical function may allow for the diagnosis and/or prognosis of an acute coronary syndrome. Particularly, the application of the at least one algorithm or mathematical function to the expression profile (data) of the human, particularly human patient, may allow for the diagnosis and/or prognosis of an acute coronary syndrome. The at least one algorithm or mathematical function may be any algorithm or mathematical function which allows for the diagnosis and/or prognosis of an acute coronary syndrome.

[0240] Preferably, the algorithm or mathematical function is obtained from a reference expression profile (data) of at least one subject, preferably of at least 2 to 40 subjects, more preferably of at least 10 to 25 subjects, and most preferably of at least 15 to 20 subjects, e.g. of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 subjects, with one known clinical condition which is an acute coronary syndrome, or which is no acute coronary syndrome (i.e. healthy/healthiness), wherein the reference expression profile is the profile of a (single) miRNA that has a nucleotide sequence that essentially corresponds (is essentially identical), preferably that corresponds (is identical), to the nucleotide sequence of the miRNA which expression profile is determinable by the means of (i), or is the profile of a set comprising at least two miRNAs that have nucleotide sequences that essentially correspond (are essentially identical), preferably that correspond (are identical), to the nucleotide sequences of the miRNAs which expression profile is determinable by the means of (i).

[0241] It is also preferred that the algorithm or mathematical function is obtained from reference expression profiles (data) of at least two subjects, preferably of at least 3 to 40 subjects, more preferably of at least 10 to 25 subjects, and most preferably of at least 15 to 20 subjects, e.g. of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 subjects, with at least two known clinical conditions (only one known clinical condition per subject), preferably at least 2 to 5, more preferably at least 2 to 4 (e.g. at least 2, 3, 4, or 5) known clinical conditions, which are acute coronary syndrome and any other known clinical condition(s), wherein the reference expression profiles are the profiles of a (single) miRNA that has a nucleotide sequence that essentially corresponds (is essentially identical), preferably that corresponds (is identical), to the nucleotide sequence of the miRNA which expression profile is determinable by the means of (i) or are the profiles of a set comprising at least two miRNAs that have nucleotide sequences that essentially correspond (are essentially identical), preferably that correspond (are identical), to the nucleotide sequences of the miRNAs which expression profile is determinable by the means of (i). It is preferred that the two known clinical conditions are an acute coronary syndrome and no acute coronary syndrome. It should be noted that said subject(s) is (are) human(s). Said subject(s) may also be designated as control subject(s).

[0242] The term "essentially corresponds (essentially identical)", as used in this aspect of the present invention, means that the miRNA(s) which expression profile is determinable by the means of (i) and the miRNA(s) of the reference expression profile may slightly differ in their nucleotide sequence, whereas said difference is so marginal that it may still allow for the diagnosis and/or prognosis of an acute coronary syndrome. Preferably, the nucleotide sequence(s) of the miRNA(s) which expression profile is determinable by the means of (i) and the nucleotide sequence(s) of the miRNA(s) of the reference expression profile differ in 1 to 5, more preferably in 1 to 3, and most preferably in 1 to 2 nucleotides, i.e. in 1, 2, 3, 4, or 5 nucleotides. It is preferred that said difference resides in 1 to 5, more preferably 1 to 3, and most preferably 1 to 2 nucleotide mutations, i.e. 1, 2, 3, 4, or 5 nucleotide mutations (e.g. substitutions, additions, insertions, and/or deletions).

[0243] Preferably, it is indicated in which type of blood sample (e.g. whole blood or blood fraction such as serum or plasma) and/or from which (control) subject(s) (e.g. gender and/or age or stage of life), the (average) reference expression profile (data), which is (are) provided with the kit, has (have) been determined. It is preferred that the expression profile

(data) of the human, particularly human patient, will be determined in the same type of blood sample and/or will be obtained from a human, particularly human patient, of the same gender and/or similar age or stage of life.

[0244] The at least one algorithm or mathematical function is preferably comprised, e.g. saved, on at least one data carrier. Said data carrier may be an electronically data carrier such as a floppy disk, a compact disk (CD), or a digital versatile disk (DVD) (e.g. for comparing tested sets of miRNA biomarkers/data with the expression profile data of a human, particularly human patient, to be diagnosed and/or prognosed). The at least one algorithm or mathematical function may further be comprised in a computer program which is saved on an electronically data carrier.

[0245] The kit may alternatively comprise an access code, preferably comprised on a data carrier, which allows the access to a database, e.g. an internet database, a centralized, or a decentralized database, where (i) the algorithm or mathematical function is comprised, or (ii) where a computer program comprising the algorithm or mathematical function can be downloaded.

[0246] More than one algorithm or mathematical function, e.g. 2, 3, 4, 5 algorithms or mathematical functions, may be comprised on one or more data carrier(s).

[0247] As described above, the kit of the present invention may also comprise both afore-mentioned alternatives

(ii) at least one reference and algorithm or mathematical function.

[0248] It is preferred that said reference and algorithm or mathematical function are comprised on at least one data carrier.

[0249] For example, the kit may comprise (i) references (data), preferably (average) reference expression profile(s) (data), which may be comprised on an information leaflet and/or on a compact disk (CD), e.g. two expression profiles (data), for example, one from a subject(s) known to be healthy and one from a subject(s) known to have an acute coronary syndrome, and (ii) algorithms or mathematical functions, which may be comprised on a compact disc (CD) and/or on a digital versatile disk (DVD), e.g. two algorithms or mathematical functions, for example, one obtained from a reference expression profile of a subject(s) known to be healthy and one obtained from a reference expression profile of a subject(s) known to have an acute coronary syndrome.

[0250] As to the reference and algorithm or mathematical function, it is also referred to the method of the second aspect of the present invention, particularly to the first and second alternative of step (ii) of the method according to the second aspect of the present invention, respectively (see above).

[0251] In a fifth aspect, the above-mentioned kits only comprise (i) the above-mentioned means for determining an expression profile of a miRNA or a set comprising at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ IDNO: 283, a fragment thereof, and a sequence having at least 80% sequence identity thereto, and only optionally comprise (ii) the above-mentioned at least one reference and/or algorithm or mathematical function, which is (are) preferably comprised on at least one data carrier. As to the preferred miRNA(s) and the preferred embodiments with respect to the means (item (i) of the kit), it is referred to the second to fourth aspect of the present invention.

[0252] Cardiac Troponins are currently the best validated biomarkers for the diagnosis of the infarct size of AMI. However, measured amounts of Troponin proteins are usually not released from damaged myocardium before 4 to 8 hours after onset of symptoms making an early biomarker based diagnosis of AMI rather difficult. Thus, a plurality of AMI patients will still be Troponin-negative during physical examination although AMI already occurred. The inventors of the present invention surprisingly found that the expression levels of three miRNAs, namely hsa-miR-145 (SEQ ID NO: 181), hsa-miR-223 (SEQ ID NO: 240), and hsa-miR-30c (SEQ ID NO: 241) directly correlate with infarct size estimated by Troponin T release. Said miRNAs are significantly up-regulated in AMI and show high correlation to Troponin T levels. Said miRNAs are also earlier detectable in human blood than Troponin. Accordingly, hsa-miR-145 (SEQ ID NO: 181), hsa-miR-223 (SEQ ID NO: 240), and hsa-miR-30c (SEQ ID NO: 241) are biomarkers in order to predict/estimate heart infarct size of a human patient.

[0253] Thus, in a sixth aspect, the present invention provides (the use of) a polynucleotide for detecting a miRNA or a set comprising at least two polynucleotides for detecting a set comprising at least two miRNAs for predicting, estimating and/or determining the heart infarct size, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 181 (hsa-miR-145), SEQ ID NO: 240 (hsa-miR-223), and SEQ ID NO: 241 (hsa-miR-30c).

[0254] Said polynucleotide(s) (probe(s)) may also be present as polynucleotide fragments, polynucleotide variants, or polynucleotide fragment variants. As to the definition of said polynucleotide fragments, polynucleotide variants, or polynucleotide fragment variants, it is referred to the first aspect of the present invention.

[0255] In a seventh aspect, the present invention relates to a miRNA or a set comprising at least two miRNAs as biomarker(s) for the diagnosis and/or prognosis of an acute coronary syndrome, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1

to 283. In a preferred embodiment, the present invention relates to a miRNA or a set comprising at least two miRNAs as biomarker(s) for the diagnosis and/or prognosis of an acute coronary syndrome, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to 153. In a particularly preferred embodiment, said miRNA set comprises at least one further miRNA, wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to 241. In another preferred embodiment, the present invention relates to a miRNA as biomarker for the diagnosis and/or prognosis of an acute coronary syndrome, wherein the nucleotide sequence of said miRNA is selected from the list of Figure 29, or the present invention relates to a set comprising at least two miRNAs as biomarkers for the diagnosis and/or prognosis of an acute coronary syndrome, wherein the nucleotide sequences of said miRNAs are selected from one or more sets listed in Figure 28 and/or Figure 30.

[0256] In a further aspect, the present invention provides a method for predicting, estimating and/or determining the heart infarct size comprising the steps of:

- (i) determining an expression profile of a miRNA or a set comprising, essentially consisting of, or consisting of at least two miRNAs, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152 or 153 miRNAs, in a blood sample from a human, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, particularly of SEQ ID NO: 181 (hsa-miR-145), SEQ ID NO: 240 (hsa-miR-223), and SEQ ID NO: 241 (hsa-miR-30c), a fragment thereof, and a sequence having at least 80% sequence identity thereto, and
- (ii) comparing said miRNA expression profile to a reference, wherein the comparison of said expression profile to said reference allows for predicting, estimating and/or determining heart infarct size.

[0257] As to the definition of the reference, expression profile, the miRNA fragment, miRNA variant, or miRNA fragment variant mentioned above, it is referred to the second aspect of the present invention.

[0258] In another further aspect, the present invention relates to a method for diagnosing and/or prognosing of an acute coronary syndrome comprising the steps of:

- (i) providing a polynucleotide according to the first aspect of the present invention for detecting a miRNA representative for an acute coronary syndrome in a human blood sample or a set comprising at least two polynucleotides according to the first aspect of the present invention for detecting a set comprising at least two miRNAs representative for an acute coronary syndrome in a human blood sample, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, particularly of SEQ ID NO: 1 to SEQ ID NO: 153, a fragment thereof, and a sequence having at least 80% sequence identity thereto,
- (ii) using the polynucleotide(s) provided in (i) for determining an miRNA expression profile in a blood sample from a human with an unknown clinical condition,
- (iii) comparing said expression profile to a reference,
- (iv) diagnosing or prognosing the clinical condition of the human individual on the basis of said comparison.

[0259] In preferred embodiments, the above-mentioned set of miRNAs comprises at least one further miRNA (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, or 88 miRNA(s)), wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to 241, a fragment thereof, and a sequence having at least 80% sequence identity thereto, particularly in order to complement a set comprising at least two miRNAs having nucleotide sequences selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153.

[0260] The term "human with an unknown clinical condition" refers to a human which may be a healthy or may be diseased, e.g. suffer from an acute coronary syndrome (e.g. myocardial infarction or Unstable angina (UA)) or suffer from another disease not tested/known. It also refers to a human which may suffer from a specific type of myocardial infarction, namely from non-ST segment elevation myocardial infarction (NSTEMI), or from ST segment elevation myocardial infarction (STEMI). It may further refer to a human that will develop the above-mentioned syndrome as the inventors of the present invention surprisingly found that miRNAs representative for an acute coronary syndrome are already present in the blood before an acute coronary syndrome occurs or during the early stage of myocardial injury.

[0261] As to the definition of said miRNA fragments, miRNA variants, or miRNA fragment variants, it is referred to the second aspect of the present invention. As to the reference and preferred embodiments of said reference, the preferred embodiments of the blood sample and the definition of an expression profile, it is also referred to the second aspect of the present invention.

[0262] In other aspects, the present invention is composed of the following:

In a further aspect of the invention sets of at least two miRNAs for diagnosing and/or prognosing of an acute coronary syndrome in a blood sample from a human are disclosed.

[0263] In order to be able to better discriminate, for example, between two or more clinical conditions, e.g. presence of acute coronary syndrome and absence of acute coronary syndrome (e.g. healthy controls), for a defined set (signature) of miRNA biomarkers, the inventors of the present invention applied a machine learning approach (e.g. t-test, AUC, support vector machine, hierarchical clustering, or k-means) which leads to an algorithm or a mathematical function that is trained by reference data (i.e. data of reference miRNA expression profiles from the two or more clinical conditions, e.g. presence of acute coronary syndrome and absence of acute coronary syndrome, for the defined set (signature) of miRNA markers) to discriminate between the two or more statistical classes (i.e. two or more clinical conditions), e.g. presence of acute coronary syndrome and absence of acute coronary syndrome.

[0264] The inventors of the present invention surprisingly found that this approach yields miRNA sets (signatures) that can predict or determine with very high diagnostic accuracy, specificity and sensitivity acute coronary syndrome in a human patient. Said miRNA sets (Set No 1-1005, Figure 28) comprise at least two miRNAs.

[0265] An exemplarily approach to arrive at miRNA sets (signatures) that correlate with the presence of an acute coronary syndrome is summarized below.

Step 1: Total RNA (or subfractions thereof) is extracted from a blood (including plasma, serum, PBMC or other blood fractions) samples of human subjects with acute coronary syndrome and controls using suitable kits and/or purification methods.

Step 2: From the respective sample, the quantity (expression level) of at least two miRNAs selected from the group of SEQ ID NO: 1 to SEQ ID NO: 279 is measured using experimental techniques. These techniques include, but are not restricted to, array based approaches, amplification methods (PCR, RT-PCR, or qPCR), sequencing, next generation sequencing, and/or mass spectroscopy.

Step 3: In order to gather information on the diagnostic/prognostic value and the redundancy of each of the single miRNA biomarkers, mathematical methods are applied. These methods include, but are not restricted to, basic mathematic approaches (e.g. Fold Quotients, Signal-to-Noise ratios, Correlation), statistical methods as hypothesis tests (e.g. t-test, Wilcoxon-Mann-Whitney test), the Area under the Receiver operator Characteristics Curve, information theory approaches, (e.g. the Mutual Information, Cross-entropy), probability theory (e.g. joint and conditional probabilities) or combinations and modifications of the previously mentioned methods.

Step 4: The information gathered in step 3) is used to estimate for each miRNA biomarker the diagnostic content or value. Usually, however, this diagnostic value is too small to get a highly accurate diagnosis with accuracy rates, specificities and sensitivities beyond the 80% barrier. The diagnostic content of the miRNAs suitable for diagnosing/prognosing an acute coronary syndrome is listed in Figure 29

Step 5: In order to increase the performance for diagnosing/prognosing of individuals suffering from acute coronary syndrome, more than one miRNA biomarker needs to be employed. Thus statistical learning / machine learning / bioinformatics / computational approaches are applied for set selection in order to select/define sets of miRNA biomarkers that are tailored for the detection of an acute coronary syndrome. These techniques include, but are not restricted to, Wrapper subset selection techniques (e.g. forward step-wise, backward step-wise, combinatorial approaches, optimization approaches), filter subset selection methods (e.g. the methods mentioned in Step 3), principal component analysis, or combinations and modifications of such methods (e.g. hybrid approaches).

Step 6: The subsets, selected/defined in Step 5, which may range from only a small number (at least two for the set) to all measured biomarkers, are then used to carry out a diagnosis/prognosis of an acute coronary syndrome. To this end, statistical learning / machine learning / bioinformatics / computational approaches are applied that include but are not restricted to any type of supervised or unsupervised analysis: classification techniques (e.g. naive Bayes, Linear Discriminant Analysis, Quadratic Discriminant Analysis Neural Nets, Tree based approaches, Support Vector Machines, Nearest Neighbour Approaches), Regression techniques (e.g. linear Regression, Multiple Regression, logistic regression, probit regression, ordinal logistic regression ordinal Probit-Regression, Poisson Regression, negative binomial Regression, multinomial logistic Regression, truncated regression), Clustering techniques (e.g. k-means clustering, hierarchical clustering, PCA), Adaptations,

extensions, and combinations of the previously mentioned approaches.

Step 7: By combination of subset selection (Step 5) and machine learning approaches (Step 6) an algorithm or a mathematical function for diagnosing/prognosing acute coronary syndrome is obtained. This algorithm or mathematical function is applied to a miRNA expression profile (miRNA expression profile data) of an individual (patient) to be diagnosed for an acute coronary syndrome.

[0266] Polynucleotides are disclosed for detecting a set comprising at least two miRNAs for diagnosing and/or prognosing of an acute coronary syndrome in a blood sample from a human. The said sets of at least two miRNAs are selected from the sets (Set No. 1 - 1005) listed in Figure 28.

[0267] It is understood that the said sets of polynucleotides are complementary to the sets of miRNAs (Set No. 1 - 1005) for diagnosing and/or prognosing of an acute coronary syndrome in a blood sample from a human and/or are fragments of these and/or have at least 80% sequence identity to these sequences.

[0268] The individual sets of polynucleotides for detecting a set comprising at least two miRNAs may also be combined with each other, e.g. polynucleotides for detecting Set No.1 with polynucleotides for detecting Set No.2, polynucleotides for detecting Set No.2 with polynucleotides for detecting Set No.3, polynucleotides for detecting Set No.1 with polynucleotides for detecting Set No.2 and Set No. 3, polynucleotides for detecting Set No.3 with polynucleotides for detecting Set No.5 and Set No. 8, etc.

[0269] In further embodiment, sets of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 polynucleotides are disclosed for detecting sets comprising at least two miRNAs for diagnosing and/or prognosing of an acute coronary syndrome in a blood sample from a human, which are selected from one or more sets (Set No. 1 - 1005) listed in Figure 28.

[0270] In a further embodiment, a method for diagnosing and/or prognosing of an acute coronary syndrome is disclosed, comprising the steps of:

(i) determining an expression profile of a set comprising at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, wherein the nucleotide sequences of said miRNAs are selected from one or more sets (Set No. 1 - 1005) listed in Figure 28

(ii) comparing said expression profile to a reference, wherein the comparison of said expression profile to said reference allows for the diagnosis and/or prognosis of an acute coronary syndrome, and/or applying an algorithm or a mathematical function to said expression profile, wherein the application of said algorithm or mathematical function to said expression profile allows for the diagnosis and/or prognosis of an acute coronary syndrome.

[0271] In a further embodiment, a method for diagnosing and/or prognosing of an acute coronary syndrome is disclosed, comprising the steps of:

(i) determining an expression profile of a set comprising 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more miRNAs representative for an acute coronary syndrome in a blood sample from a human, wherein the nucleotide sequences of said miRNAs comprise at least one set (Set No. 1 - 1005) listed in Figure 28

(ii) comparing said expression profile to a reference, wherein the comparison of said expression profile to said reference allows for the diagnosis and/or prognosis of an acute coronary syndrome, and/or applying an algorithm or a mathematical function to said expression profile, wherein the application of said algorithm or mathematical function to said expression profile allows for the diagnosis and/or prognosis of an acute coronary syndrome.

[0272] In a further embodiment, a kit for diagnosing and/or prognosing of an acute coronary syndrome is disclosed comprising:

(i) means for determining an expression profile of a set comprising at 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more miRNAs representative for an acute coronary syndrome in a blood sample from a human, wherein the nucleotide sequences of said miRNAs comprise at least one set (Set No. 1 - 1005) listed Figure 28 and a sequences having at least 80% sequence identity thereto; and

(ii) at least one reference.

[0273] In a further embodiment, a kit for diagnosing and/or prognosing of an acute coronary syndrome is disclosed comprising:

(i) means for determining an expression profile of a set comprising at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, wherein the nucleotide sequences of said miRNAs are selected from the sets (Set No. 1 - 1005) listed Figure 28 and a sequences having at least 80% sequence identity thereto; and

(ii) at least one reference.

[0274] In summary, this aspect of the present invention is composed of the following:

1. A set of polynucleotides for detecting a set comprising at least two miRNAs for diagnosing and/or prognosing of an acute coronary syndrome in a blood sample from a human, wherein the nucleotide sequences of said miRNAs are selected from the group of sets (Set No. 1 - 1005) listed in Figure 28.

2. The set comprising polynucleotides of item 1, wherein

(i) the polynucleotides comprised in the set are complementary to the miRNAs comprised in the set according to claim 1,

(ii) the polynucleotides comprised in the set are fragments of the polynucleotides comprised in the set according to (i), or

(i) polynucleotide fragments according to (ii), or the polynucleotides comprised in the set have at least 80% sequence identity to the polynucleotide sequences of the polynucleotides comprised in the set according to (i) or polynucleotide fragments comprised in the set according to (ii).

3. A method for diagnosing and/or prognosing of an acute coronary syndrome comprising the steps of:

(i) determining an expression profile of a set comprising at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, wherein the nucleotide sequences of said miRNAs are selected from the sets (Set No. 1- 1005) listed in Figure 28, fragments thereof, and sequences having at least 80% sequence identity thereto, and

(ii) comparing said expression profile to a reference, wherein the comparison of said expression profile to said reference allows for the diagnosis and/or prognosis of an acute coronary syndrome.

4. The method of item 3, wherein the reference is obtained from reference expression profiles of at least two humans with at least two known clinical conditions from which at least one is an acute coronary syndrome, wherein the reference expression profiles are the profiles of a set comprising at least two miRNAs that have nucleotide sequences that correspond to the nucleotide sequences selected in step (i).

5. The method of items 3 or 4, wherein the comparison to the reference comprises the application of an algorithm or mathematical function, preferably obtained using a machine learning approach.

6. A method of items 3 to 5, wherein in step (i) the set comprising at least two polynucleotides according to claims 1 to 2 is used for determining expression profiles of a set comprising at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human.

7. Means for diagnosing and/or prognosing of an acute coronary syndrome comprising set comprising at least two polynucleotides according to item 1 to 2.

8. The means of item 7, wherein said means comprise a biochip comprising a set comprising at least two polynucleotides according to item 1 to 2.

9. A kit for diagnosing and/or prognosing of an acute coronary syndrome comprising

(i) means for determining expression profiles of a set comprising at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, wherein the nucleotide sequence of said miRNAs are selected from the sets (Set No. 1- 1005) listed Figure 28 and a sequences having at least 80% sequence identity thereto; and

(ii) at least one reference.

10. The kit of item 9, wherein said kit comprises the means of items 7 or 8.

11. A set of polynucleotides for detecting a set comprising at least two miRNAs for predicting, estimating and/or determining the heart infarct size, wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 181 (hsa-miR-145) and SEQ ID NO: 241 (hsa-miR-30c).

[0275] The present invention as described herein is summarized as follows:

1. A polynucleotide for detecting a miRNA or a set comprising at least two polynucleotides for detecting a set comprising at least two miRNAs for diagnosing and/or prognosing of an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide se-

quences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283.

2. The polynucleotide or set comprising polynucleotides of item 1, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153.

3. The polynucleotide or set comprising polynucleotides of items 1 or 2, wherein

(i) the polynucleotide is complementary to the miRNA according to items 1 or 2, or the polynucleotides comprised in the set are complementary to the miRNAs comprised in the set according to items 1 or 2,

(ii) the polynucleotide is a fragment of the polynucleotide according to (i), or the polynucleotides comprised in the set are fragments of the polynucleotides comprised in the set according to (i), or

(iii) the polynucleotide has at least 80% sequence identity to the polynucleotide sequence of the polynucleotide according to (i) or polynucleotide fragment according to (ii), or the polynucleotides comprised in the set have at least 80% sequence identity to the polynucleotide sequences of the polynucleotides comprised in the set according to (i) or polynucleotide fragments comprised in the set according to (ii).

4. The polynucleotides of items 1 to 3, wherein said polynucleotides are for detecting a set comprising at least 3, 4, 5, 7, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 75, 100 miRNAs, or comprising 153 miRNAs, and wherein the nucleotide sequences of said miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153.

5. The polynucleotides of items 1 to 4, wherein

(i) the nucleotide sequences of the at least 2 miRNAs comprised in the set have SEQ ID NO: 1 and SEQ ID NO: 2,

(ii) the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 3,

(iii) the nucleotide sequences of the at least 4 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 4,

(iv) the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 5,

(v) the nucleotide sequences of the at least 7 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 7,

(vi) the nucleotide sequences of the at least 10 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 10,

(vii) the nucleotide sequences of the at least 15 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 15,

(viii) the nucleotide sequences of the at least 20 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 20,

(ix) the nucleotide sequences of the at least 25 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 25,

(x) the nucleotide sequences of the at least 30 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 30,

(xi) the nucleotide sequences of the at least 35 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 35,

(xii) the nucleotide sequences of the at least 40 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 40,

(xiii) the nucleotide sequences of the at least 50 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 50,

(xiv) the nucleotide sequences of the at least 60 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 60,

(xv) the nucleotide sequences of the at least 70 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 70,

(xvi) the nucleotide sequences of the at least 75 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 75,

(xvii) the nucleotide sequences of the at least 100 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 100, or

(xviii) the nucleotide sequences of the 153 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 153.

6. The polynucleotides of items 1 to 4, wherein

(i) the nucleotide sequences of the at least 2 miRNAs comprised in the set have SEQ ID NO: 1 and SEQ ID NO: 2,

(ii) the nucleotide sequences of the at least 2 miRNAs comprised in the set have SEQ ID NO: 3 and SEQ ID NO: 4,

(iii) the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7,

(iv) the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10,

(v) the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 11, SEQ ID NO: 12, and SEQ ID NO: 13,

(vi) the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 14, SEQ ID NO:

15, and SEQ ID NO: 16,

(vii) the nucleotide sequences of the at least 4 miRNAs comprised in the set have SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, and SEQ ID NO: 20,

(viii) the nucleotide sequences of the at least 4 miRNAs comprised in the set have SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, and SEQ ID NO: 24, or

(ix) the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30.

7. The polynucleotides of items 2 to 6, wherein said polynucleotides are for detecting a set comprising at least one further miRNA, wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241.

8. The polynucleotides of items 1 to 7, wherein the nucleotide sequences of said miRNAs are selected from one or more sets listed in Figure 28 and/or Figure 30.

9. The polynucleotide of items 1 to 3, wherein said polynucleotide is for detecting a nucleotide sequence of a miRNA selected from the group consisting of SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a).

10. The polynucleotide of item 9, wherein said polynucleotide is for detecting the nucleotide sequence of the miRNA of SEQ ID NO: 1 (hsa-miR-1291).

11. A method for diagnosing and/or prognosing of an acute coronary syndrome comprising the steps of:

(i) determining an expression profile of a miRNA or a set comprising at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, a fragment thereof, and a sequence having at least 80% sequence identity thereto, and

(ii) comparing said expression profile to a reference, wherein the comparison of said expression profile to said reference allows for the diagnosis and/or prognosis of an acute coronary syndrome and/or applying an algorithm or a mathematical function to said expression profile, wherein the application of said algorithm or mathematical function to said expression profile allows for the diagnosis and/or prognosis of an acute coronary syndrome.

12. The method of item 11, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, a fragment thereof, and a sequence having at least 80% sequence identity thereto.

13. The method of items 11 or 12, wherein the algorithm or mathematical function is obtained from a reference expression profile of at least one subject with one known clinical condition which is an acute coronary syndrome, or which is no acute coronary syndrome, wherein the reference expression profile is the profile of a miRNA that has a nucleotide sequence that corresponds to the nucleotide sequence of the miRNA of step (i) or is the profile of a set comprising at least two miRNAs that have nucleotide sequences that correspond to the nucleotide sequences of the miRNAs of step (i).

14. The method of items 11 to 13, wherein the algorithm or mathematical function is obtained from reference expression profiles of at least two subjects with at least two known clinical conditions which are an acute coronary syndrome and any other known clinical condition(s), wherein the reference expression profiles are the profiles of a miRNA that has a nucleotide sequence that corresponds to the nucleotide sequence of the miRNA of step (i) or are the profiles of a set comprising at least two miRNAs that have nucleotide sequences that correspond to the nucleotide sequences of the miRNAs of step (i).

15. The method of item 14, wherein the two known clinical conditions are an acute coronary syndrome and no acute coronary syndrome.

16. The method of items 11 to 15, wherein the algorithm or mathematical function is obtained using a machine learning approach.

17. The method of item 16, wherein the machine learning approach involves the following steps:

(i) inputting the reference expression profile(s) of (a) subject(s) with the known clinical condition of an acute coronary syndrome and/or with any other known clinical condition(s), preferably with the known clinical condition of no acute coronary syndrome, and

(ii) computing an algorithm or a mathematical function based on said reference expression profile(s) that is suitable to distinguish between the (likely) clinical condition of an acute coronary syndrome and any other (likely)

clinical condition(s), preferably the clinical condition of no acute coronary syndrome, or to decide if the clinical condition of an acute coronary syndrome or no acute coronary syndrome is present or will likely be present in said human, particularly human patient.

18. The method of items 11 to 17, wherein the reference is a reference expression profile of at least one subject with one known clinical condition which is an acute coronary syndrome, or which is no acute coronary syndrome, wherein the reference expression profile is the profile of a miRNA that has a nucleotide sequence that corresponds to the nucleotide sequence of the miRNA of step (i) or is the profile of a set comprising at least two miRNAs that have nucleotide sequences that correspond to the nucleotide sequences of the miRNAs of step (i).

19. The method of items 11 to 18, wherein the set comprises at least 3, 4, 5, 7, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 75, 100 miRNAs, or comprises 153 miRNAs, and wherein the nucleotide sequences of the miRNAs are selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153.

20. The method of items 11 to 19, wherein

- (i) the nucleotide sequences of the at least 2 miRNAs comprised in the set have SEQ ID NO: 1 and SEQ ID NO: 2,
- (ii) the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 3,
- (iii) the nucleotide sequences of the at least 4 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 4,
- (iv) the nucleotide sequences of the at least 5 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 5,
- (v) the nucleotide sequences of the at least 7 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 7,
- (vi) the nucleotide sequences of the at least 10 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 10,
- (vii) the nucleotide sequences of the at least 15 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 15,
- (viii) the nucleotide sequences of the at least 20 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 20,
- (ix) the nucleotide sequences of the at least 25 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 25,
- (x) the nucleotide sequences of the at least 30 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 30,
- (xi) the nucleotide sequences of the at least 35 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 35,
- (xii) the nucleotide sequences of the at least 40 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 40,
- (xiii) the nucleotide sequences of the at least 50 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 50,
- (xiv) the nucleotide sequences of the at least 60 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 60,
- (xv) the nucleotide sequences of the at least 70 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 70,
- (xvi) the nucleotide sequences of the at least 75 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 75,
- (xvii) the nucleotide sequences of the at least 100 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 100, or
- (xviii) the nucleotide sequences of the 153 miRNAs comprised in the set have SEQ ID NO: 1 to SEQ ID NO: 153.

21. The method of items 11 to 19, wherein

- (i) the nucleotide sequences of the at least 2 miRNAs comprised in the set have SEQ ID NO: 1 and SEQ ID NO: 2,
- (ii) the nucleotide sequences of the at least 2 miRNAs comprised in the set have SEQ ID NO: 3 and SEQ ID NO: 4,
- (iii) the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7,
- (iv) the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10,
- (v) the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 11, SEQ ID NO: 12, and SEQ ID NO: 13,
- (vi) the nucleotide sequences of the at least 3 miRNAs comprised in the set have SEQ ID NO: 14, SEQ ID NO: 15, and SEQ ID NO: 16,
- (vii) the nucleotide sequences of the at least 4 miRNAs comprised in the set have SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, and SEQ ID NO: 20,
- (viii) the nucleotide sequences of the at least 4 miRNAs comprised in the set have SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, and SEQ ID NO: 24, or
- (ix) the nucleotide sequences of the at least 6 miRNAs comprised in the set have SEQ ID NO: 25, SEQ ID NO:

26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30.

22. The method of items 12 to 21, wherein the set comprises at least one further miRNA, wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, a fragment thereof, and a sequence having at least 80% sequence identity thereto.

23. The method of items 11 to 22, wherein the nucleotide sequences of said miRNAs are selected from one or more sets listed in Figure 28 and/or Figure 30.

24. The method of item 11, wherein the miRNA is selected from the group consisting of SEQ ID NO: 16 (hsa-miR-455-3p), SEQ ID NO: 18 (hsa-miR-192*), SEQ ID NO: 2 (hsa-miR-1283), SEQ ID NO: 1 (hsa-miR-1291), SEQ ID NO: 19 (hsa-miR-767-5p), SEQ ID NO: 22 (hsa-miR-20b*), SEQ ID NO: 23 (hsa-miR-491-3p), SEQ ID NO: 29 (hsa-miR-33a), SEQ ID NO: 32 (hsa-miR-380*), and SEQ ID NO: 39 (hsa-miR-216a).

25. The method of item 24, wherein said miRNA has the SEQ ID NO: 1 (hsa-miR-1291).

26. The method of items 11 to 25, wherein in step (i) a polynucleotide or a set comprising at least two polynucleotides according to items 1 to 10 is used for determining an expression profile of a miRNA or a set comprising at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient.

27. The method of items 11 to 26, wherein the blood sample is a blood plasma sample or a blood serum sample.

28. The method of items 11 to 27, wherein the expression profile of the miRNA(s) representative for an acute coronary syndrome is determined by nucleic acid hybridization, nucleic acid amplification, polymerase extension, sequencing, mass spectroscopy or any combination thereof.

29. The method of item 28, wherein

(i) the nucleic acid hybridization is performed using a microarray/biochip, or using in situ hybridization, or

(ii) the nucleic acid amplification is performed using real-time PCR.

30. The method of items 11 to 29, wherein the reference and optionally the expression profile of the miRNA(s) representative for an acute coronary syndrome is (are) stored in a database.

31. The method of items 11 to 30, wherein the diagnosis comprises

(i) determining the occurrence/presence of an acute coronary syndrome,

(ii) monitoring the course of an acute coronary syndrome,

(iii) staging of an acute coronary syndrome,

(iv) measuring the response of an individual with an acute coronary syndrome to therapeutic intervention, and/or

(v) segmentation of individuals suffering from an acute coronary syndrome.

32. The method of items 11 to 30, wherein the prognosis comprises

(i) identifying an individual who has a risk to develop an acute coronary syndrome,

(ii) predicting/estimating the occurrence, preferably the severity of occurrence, of an acute coronary syndrome, and/or

(iii) predicting the response of an individual with an acute coronary syndrome to therapeutic intervention.

33. Means for diagnosing and/or prognosing of an acute coronary syndrome comprising a polynucleotide or a set comprising at least two polynucleotides according to items 1 to 10.

34. The means of item 33, wherein said means comprise a biochip comprising a polynucleotide or a set comprising at least two polynucleotides according to items 1 to 10.

35. A kit for diagnosing and/or prognosing of an acute coronary syndrome comprising

(i) means for determining an expression profile of a miRNA or a set comprising at least two miRNAs representative for an acute coronary syndrome in a blood sample from a human, particularly human patient, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, a fragment thereof, and a sequence having at least 80% sequence identity thereto; and

(ii) at least one reference and/or algorithm or mathematical function, preferably comprised on at least one data carrier.

36. The kit of item 35, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, a fragment thereof, and a sequence having at least 80% sequence identity thereto.

37. The kit of item 36, wherein the set comprises at least one further miRNA, wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to SEQ ID NO: 241, a fragment thereof, and a sequence having at least 80% sequence identity thereto.

38. The kit of items 35 to 37, wherein the nucleotide sequences of said miRNAs are selected from one or more sets listed in Figure 28 and/or Figure 30.

39. The kit of items 35 to 38, wherein said kit comprises the means of items 33 or 34.

40. A polynucleotide for detecting a miRNA or a set comprising at least two polynucleotides for detecting a set comprising at least two miRNAs for predicting, estimating and/or determining the heart infarct size, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 181 (hsa-miR-145), SEQ ID NO: 240 (hsa-miR-223), and SEQ ID NO: 241 (hsa-miR-30c).

41. A miRNA or a set comprising at least two miRNAs as biomarker(s) for the diagnosis and/or prognosis of an acute coronary syndrome, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to 283.

42. The miRNA or miRNA set of item 41, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to 153.

43. The miRNA set of item 42, wherein the miRNA set comprises at least one further miRNA, wherein the nucleotide sequence of said miRNA is selected from the group consisting of SEQ ID NO: 154 to 241.

44. The miRNA set of items 41 to 43, wherein the nucleotide sequences of said miRNAs are selected from one or more sets listed in Figure 28 and/or Figure 30.

BRIEF DESCRIPTION OF THE DRAWINGS

[0276]

Figure 1: MiRNA expression profiling in peripheral blood cells of AMI patients and controls. **(A)** Matrix plot showing high linear correlation of the mean expression ratios of miRNAs in AMI patients versus controls. **(B)** Histograms of the logarithm of fold changes, AUC, raw, and adjusted p-values for all screened miRNAs. The logqmedian diagram shows the logarithms of miRNA expression changes in AMI patients in comparison to controls. The expression changes are almost normally distributed between -4 and +4. The AUC for all expression values is given, the vertical blue line denotes the threshold of 0.1 and 0.9. The middle and bottom part of the figure represent histograms of adjusted p-values for the limma test and t-test. The vertical line denotes the significance threshold of 0.05.

Figure 2: Specific miRNAs are dysregulated in acute myocardial infarction. Whisker-plots showing median expression values of the five most significantly dysregulated miRNAs (miR-1291, -455-3p, -216a, -1283, and -33a) in patients with myocardial infarction (right bars) in comparison to controls (left bars).

Figure 3: miRNA-1291 predicts myocardial infarction. Receiver Operating Characteristic (ROC) analysis of miRNA-1291 to predict AMI in the study population. MiRNA-1291 is able to predict the presence of AMI with a specificity of 92.9% and a sensitivity of 85%. TP = true positives, FP = false positives.

Figure 4: MiR-30c and miR-145 levels highly correlate with Troponin T. **(A to C)** Matrix-plots showing correlation of miR-30c **(A)**, miR-145 **(B)**, and miR-223 **(C)** with peak Troponin T serum levels (left column) and Troponin T levels at day 3 (right column). hsTnT = highly sensitive Troponin T.

Figure 5: Hierarchical clustering of miRNA expression levels. Unsupervised hierarchical clustering of expression levels of the 100 most significantly dysregulated miRNAs using the Euclidian distance measure. All AMI patients cluster separately from the controls with only two outliers.

Figure 6: Complex miRNA signatures predict AMI. **(A)** ROC analysis of the complex miRNA expression signature used to predict AMI in the study population. **(B)** Representative example of a classification result using a trained SVM. The logarithm of the quotient of the probability to be an AMI sample and the probability to be a control sample for each study sample is given on the y-axis. Of all 48 samples, only 2 were misclassified, leading to an accuracy of 95%, a specificity of 100%, and a sensitivity of 90%.

Figure 7: MiRNAs for diagnosis or prognosis of an acute coronary syndrome (AMI). Experimental details : median g1 = median intensity value of the AMI patients; median g2= median intensity value of the healthy controls; qmedian= ratio of median g1 and median g2; logqmedian= log of qmedian; ttest_rawp=p-value calculated according to ttest; ttest_adj= adjusted p-value calculated according to ttest; limma_rawp=p-value calculated according to limma-test; limma_adj=adjusted p-value calculated according to limma-test; AUC= area under the curve statistics.

Figure 8: Scheme of a miRNA hybridization assay for use in the invention. The polynucleotide (miRNA capture probe) for detecting a miRNA consists of a sequence stretch which is complementary to said miRNA. Said stretch is linked to the support via its 3' end or alternatively via its 5' end (not depicted here). Each polynucleotide (miRNA capture probe) can bind the respective miRNA target sequence. The miRNA target sequence may be labeled prior to hybridization (e.g. by biotin labeling).

Figure 9: Schema of a miRNA tandem hybridization assay for use in the invention. The polynucleotide tandem or hybrid (miRNA captured tandem or hybrid probe) may consist of two DNA-based sequence stretches that may be linked to each other by a spacer element and which may be identical. The polynucleotide tandem or hybrid (miRNA captured tandem or hybrid probe) is complementary to the respective miRNA sequence. Each polynucleotide tandem or hybrid may bind two miRNA target sequences. The spacer sequence may consist of between 0 and 12 nucleotides. The miRNA target sequence may be labeled prior to hybridization (e.g. by biotin labeling).

Figure 10: miRNA RAKE-Assay for use in the invention (PT Nelson et al., Nature methods, 2004, 1 (2), 1). The polynucleotide (miRNA capture probe) for detecting a miRNA consists of a sequence stretch and an elongation element. The polynucleotide (miRNA capture probe) is oriented 5'→3', presenting a free terminal 3'-OH. The miRNA probe sequence stretch is complementary to the miRNA target sequence. The elongation sequence can be freely chosen and is typically between 1 to 12 nucleotides long, preferably is a homomeric sequence. Each miRNA probe can bind a respective miRNA target sequence. miRNA target sequences are not labeled prior to hybridization. The labeling occurs after hybridization during elongation by a polymerase extension reaction.

Figure 11: miRNA MPEA-Assay for use in the invention (Vorwerk S. et al., Microfluidic based enzymatic on-chip labeling of miRNAs, N. Biotechnol. 2008; 25(2-3): 142-9. Epub, 2008, Aug 20). The polynucleotide (miRNA capture probe) for detecting a miRNA consists of a sequence stretch and an elongation element. The polynucleotide (miRNA capture probe) is oriented 3'→5', presenting a free terminal 5'-OH. The miRNA probe sequence stretch is complementary to the miRNA target sequence. The elongation sequence can be freely chosen and is typically between 1 to 12 nucleotides long, preferably is a homomeric sequence. Each miRNA probe can bind a respective miRNA target sequence. miRNA target sequences are not labeled prior to hybridization. The labeling occurs after hybridization during elongation by a polymerase extension reaction. The biochip is reusable after target removal/elongated target.

Figure 12: Listing of miRNAs for diagnosis or prognosis of an acute coronary syndrome (AMI). The miRNAs sequences are based on miRBase version 14.0.

Figure 13: Classification plot; classification of patients with AMI from healthy controls on the basis of the 2 miRNA-Biomarkers (SEQ ID NO 1-2) leading on average to accuracy of 70%, specificity of 72% and sensitivity of 68%. (numbers without border = healthy controls, numbers within squares = AMI patients and with 1, 2, 3, 4, 5 assigning control samples from 5 independent institutions).

Figure 14: Classification plot; classification of patients with AMI from healthy controls on the basis of the 4 miRNA-Biomarkers (SEQ ID NO 1-4) leading on average to accuracy of 85.5%, specificity of 89% and sensitivity of 82% (numbers without border = healthy controls, numbers within squares = AMI patients and with 1, 2, 3, 4, 5 assigning control samples from 5 independent institutions).

Figure 15: Classification plot; classification of patients with AMI from healthy controls on the basis of the 6 miRNA-Biomarkers (SEQ ID NO 1-6) leading on average to accuracy of 79.5%, specificity of 83% and sensitivity of 76%. (numbers without border = healthy controls, numbers within squares = AMI patients and with 1, 2, 3, 4, 5 assigning control samples from 5 independent institutions).

Figure 16: Classification plot; classification of patients with AMI from healthy controls on the basis of the 8 miRNA-Biomarkers (SEQ ID NO 1-8) leading on average to accuracy of 81.5%, specificity of 83% and sensitivity of 80%. (numbers without border = healthy controls, numbers within squares = AMI patients and with 1, 2, 3, 4, 5 assigning control samples from 5 independent institutions).

Figure 17: Classification plot; classification of patients with AMI from healthy controls on the basis of the 10 miRNA-Biomarkers (SEQ ID NO 1-10) leading on average to accuracy of 82.5%, specificity of 88% and sensitivity of 77% (numbers without border = healthy controls, numbers within squares = AMI patients and with 1, 2, 3, 4, 5 assigning control samples from 5 independent institutions).

Figure 18: Classification plot; classification of patients with AMI from healthy controls on the basis of the 50 miRNA-Biomarkers (SEQ ID NO 1-50) leading on average to accuracy of 83%, specificity of 86% and sensitivity of 80%. (numbers without border = healthy controls, numbers within squares = AMI patients and with 1, 2, 3, 4, 5 assigning control samples from 5 independent institutions).

Figure 19: Classification plot; classification of patients with AMI from healthy controls on the basis of the 80 miRNA-Biomarkers (SEQ ID NO 1-80) leading on average to accuracy of 85.5%, specificity of 93% and sensitivity of 78%. (numbers without border = healthy controls, numbers within squares = AMI patients and with 1, 2, 3, 4, 5 assigning control samples from 5 independent institutions)

Figure 20: Classification plot; classification of patients with AMI from healthy controls on the basis of the 100 miRNA-Biomarkers (SEQ ID NO 1-100) leading on average to accuracy of 85%, specificity of 90% and sensitivity of 80%. (numbers without border = healthy controls, numbers within squares = AMI patients and with 1, 2, 3, 4, 5 assigning control samples from 5 independent institutions)

Figure 21: Diagram describing the general approach for determining miRNA signatures for use as biomarkers in the diagnosis and/or prognosis of an acute coronary syndrome.

Figure 22: MiRNA expression profiling in peripheral blood cells of AMI patients and controls. (A) Matrix plot showing

high linear correlation of the mean expression ratios of miRNAs in AMI patients (n=20) versus controls (n=20). (B) Histograms of the logarithm of fold changes, AUC, raw, and adjusted p-values for all screened miRNAs. The logq-median diagram shows the logarithms of miRNA expression changes in AMI patients in comparison to controls. The expression changes are distributed between -4 and +4. The AUC for all expression values is given, the vertical blue line denotes the threshold of 0.1 and 0.9. The middle and bottom part of the figure represent histograms of adjusted p-values for the limma test and t-test. The vertical blue line denotes the significance threshold of 0.05.

Figure 23: Specific miRNAs are dysregulated in acute myocardial infarction. Bar graphs showing mean expression values of (A) the 20 most significantly downregulated and (B) upregulated miRNAs in patients with acute myocardial infarction (n=20; dark grey bars) in comparison to controls (n=20; light grey bars).

Figure 24: Single miRNAs predict myocardial infarction. Receiver Operating Characteristic (ROC) analysis of miRNA-1291 and miRNA-663b to predict AMI in the study population. (A) MiRNA-1291 is able to predict the presence of AMI with a specificity of 85% and a sensitivity of 85%, while miRNA-663b shows a specificity of 95% and a sensitivity of 90%. TP = true positives, FP = false positives.

Figure 25: MiR-145 and miR-30c levels correlate with Troponin T release. Matrix-plots showing correlation of miR-145 (A) and miR-30c (B) with peak Troponin T serum levels (left column) and Troponin T levels at day 3 (right column). (C) Absolute expression values ($\pm$ SEM) of miR-145 and miR-30c in AMI patients and controls. hsTnT = highly sensitive Troponin T.

Figure 26: Clusters of circulating miRNAs in patients with AMI versus controls. Unsupervised hierarchical clustering of expression levels of the 20 most dysregulated miRNAs using the Euclidian distance measure. AMI patients (n=20) and control subjects (n=20) cluster separately with only three outliers, showing that distinct miRNA patterns are unique for cases and controls, respectively.

Figure 27: Complex miRNA signatures predict AMI. (A) Classification plot demonstrating that a multi-marker signature increases test accuracy, specificity, and sensitivity depending upon the number of miRNAs that compose the diagnostic signature. (B) ROC analysis of the complex miRNA expression signature used to predict AMI in the study population. (C) Representative example of a classification result using a trained SVM. The logarithm of the quotient of the probability to be an AMI sample and the probability to be a control sample for each study sample is given on the y-axis. Of all 40 samples, only 3 were misclassified, leading to an accuracy of 93%, a specificity of 96%, and a sensitivity of 90% (AUC = 0.99).

Figure 28: Sets (Set No. 1-1005) of least two miRNAs for diagnosing and/or prognosing of an acute coronary syndrome in a blood sample from a human (with Acc = accuracy, Sens = sensitivity, Spec = specificity in percent). Subjects without acute coronary syndrome that underwent routine coronary angiography were selected as the healthy controls.

Figure 29: miRNAs for diagnosis or prognosis of an acute coronary syndrome (AMI). Experimental details : median g1 = median intensity value of the AMI patients; median g2 = median intensity value of the healthy controls; qmedian = ratio of median g1 and median g2; logqmedian = log of qmedian; ttest_rawp = p-value calculated according to ttest; ttest_adjp = adjusted p-value calculated according to ttest; limma_rawp = p-value calculated according to limma-test; limma_adjp = adjusted p-value calculated according to limma-test; AUC = area under the curve statistics. Subjects without acute coronary syndrome that underwent routine coronary angiography were selected as the healthy controls.

Figure 30: Predetermined set of microRNAs for diagnosis or prognosis of acute myocardial infarction. High accuracy (Acc) of 90.48% to 99.53 % for classification between patients suffering from acute myocardial infarction and healthy controls was obtained when defined sets of 2 - 7 miRNAs (Set No. 2000-2011) were employed.

EXAMPLES

[0277] The Examples are designed in order to further illustrate the present invention and serve a better understanding. They are not to be construed as limiting the scope of the invention in any way.

EXAMPLE: 1

Materials and Methods

Patients and controls

[0278] In the present study, 20 patients with acute ST Elevation Myocardial Infarction (STEMI) were included. Acute myocardial infarction (AMI) was diagnosed according to the ESC/AHA redefined guidelines using Troponin-T as key biomarker. Vessel occlusion by an underlying thrombotic event as cause of AMI was confirmed in all patients by early coronary angiography. As control served miRNA profiles from 22 control subjects, which were recruited in the "Biomarker Discovery Center Heidelberg - Pilot Study". To exclude bias due to sample origin or treatment, 7 controls undergoing

routine coronary angiography were additionally recruited. The analysis of blood from patients and healthy subjects has been approved by local ethics committees and participants have given written informed consent. Blood from patients with AMI was obtained briefly before coronary angiography. Serial Troponin T levels were assessed using the Elecsys highly sensitive Troponin T assay (Roche, Germany) [17].

MiRNA expression profiling from peripheral blood samples

[0279] MiRNA expression profiling was performed by personnel blinded to patient characteristics. 5 ml blood was collected from study subjects in PAXgene Blood RNA tubes (BD, USA) and stored at 4°C until RNA was extracted. Total RNA was isolated from blood cells using the miRNeasy Mini Kit (Qiagen, Germany) and stored at -80°C. Samples were analyzed with the Geniom Real-time Analyzer (febit group, Germany) using the Geniom Biochip miRNA homo sapiens. Each array contains 7 replicates of 866 miRNAs and miRNA star sequences as annotated in the Sanger miRBase 12.0 [18]. Sample labelling with biotin was carried out by microfluidic-based enzymatic on-chip labelling of miRNAs (MPEA) as described before [19].

[0280] Following hybridization for 16 hours at 42°C the biochip was washed and signals were measured. The resulting images were evaluated using the Geniom Wizard Software (febit group, Germany). For each array, the median signal intensity of all features was extracted from the raw data file such that for each miRNA seven intensity values were calculated corresponding to each replicate on the array. Following background correction, the seven replicate intensity values of each miRNA were summarized by their median value. To normalize the data across different arrays, quantile normalization was applied and all further analyses were carried out using the normalized and background subtracted intensity values [19]. To this end, we removed those miRNAs having an overall median signal intensity of less than 10. The final data set contained expression levels of 708 miRNAs.

Statistical analysis

[0281] After ensuring approximate normal distribution of the measured intensity values using Shapiro-Wilk test, we carried out parametric t-test (unpaired, two-tailed) for each miRNA separately to detect miRNAs with different expression levels between study groups. The resulting p-values were adjusted for multiple testing by Benjamini-Hochberg equation [20].

[0282] In addition to the single biomarker analysis, classification of samples using miRNA patterns was carried out using Support Vector Machines (SVM) as implemented in the R e1071 package (<http://www.r-project.org>). In particular, different kernel SVMs (linear, polynomial, sigmoid, radial basis function) were evaluated, where the cost parameter was sampled from 0.01 to 10 in decimal powers. The measured miRNA profiles were classified using 20 repetitions of standard 10-fold cross-validation. The classification has been carried out using equal class sizes. Since we analyzed 29 controls and 20 patients, in each cross-validation run 20 of 29 control samples were selected randomly. To detect the most suitable set of miRNAs that achieves the best discriminatory performance, a feature extraction (subset selection) method relying on t-test p-values was used. In detail, the following filter technique was applied: The s miRNAs with lowest p-values in the t-test were computed on the training set in each fold of the cross validation, where s was sampled from 1 to 866 in regular intervals. The respective subset was used to train the SVM and to carry out the prediction of the test samples. The mean accuracy, specificity, and sensitivity were calculated for each subset size. To check for overtraining we applied permutation tests. Here, we sampled the class labels randomly and carried out classifications using the permuted class labels. All statistical analyzes were performed using R.

Results

Acute ST Elevation Myocardial Infarction leads to dysregulation of specific miRNAs

[0283] We analyzed the expression of 866 miRNAs and miRNA star sequences in blood cells of the 20 patients with acute myocardial infarction (AMI) and 29 healthy control subjects. Mean age in AMI patients was 59.3 ± 14 years and in controls 44.4 ± 20.4 years ($p < 0.01$). 20% of the AMI and 59% of the control population were female, respectively. According to ECG criteria 15 patients showed signs of inferior/posterior wall infarction and 5 of anterior wall infarction. The mean hsTnT on admission was 363.5 ± 572.5 pg/ml. 9 patients (45%) with AMI had Troponin T levels of < 50 pg/ml, and 2 of them were below 14 pg/ml on admission. Because both, gender and age distribution significantly differed between AMI patients and controls, we first analyzed if gender or age impacts on miRNA profiles. However, neither gender nor age had a statistically significant impact on miRNA expression.

[0284] To test for the overall correlation of miRNA expression between cases and controls, we computed the median expression of all miRNAs in both groups on a logarithmic scale. As shown in the scatter plot in **Figure 1A**, both groups had a high correlation coefficient of 0.847 and data variance as low as 0.002. After ensuring an approximate normal

distribution using Shapiro-Wilk test, we performed two-tailed unpaired t-tests for each miRNA. The respective p-values were adjusted for multiple testing by the Benjamini-Hochberg approach. In total, we detected 67 miRNAs to be significantly dysregulated in blood cells from AMI patients in comparison to controls at an adjusted significance (alpha) level of $p < 0.001$. Histogram plots of the logarithm of fold ratios, the raw t-test p-values and the adjusted p-values are presented in **Figure 1B**. A complete list of 241 dysregulated miRNAs is given in **Figure 7**. Notably, from the 67 significantly dysregulated miRNAs only 8 (12%) were up-regulated while 59 (88%) were down-regulated in AMI patients. The five most significantly dysregulated miRNAs were miR-1291, miR-455-3p, miR-216a, miR-1283, and miR-33a, which were all down-regulated in comparison to controls (**Figure 2** and **Table 1**). Two cardiac miRNAs, namely miR-21 and miR-1 were both up-regulated in myocardial infarction (1.6 fold up-regulation of miR-21, $p = 0.02$ and 4.4 fold up-regulation of miR-1, $p = 0.067$).

Table 1: Most significantly dysregulated miRNAs in AMI patients.

miRNA	Mean expression in AMI patients	Mean expression in controls	Fold change	Adjusted p-value
miR-1283	1.00	112.38	0.01	2.27E-06
miR-455-3p	56.93	184.95	0.31	3.12E-06
miR-33a	39.07	126.26	0.31	3.12E-06
miR-216a	45.15	199.40	0.23	3.23E-06
miR-1291	20.21	141.03	0.14	3.30E-06
miR-20b*	19.07	70.09	0.27	4.51E-06
miR-380*	32.79	86.91	0.38	5.60E-06
miR-491-3p	1.00	92.62	0.01	7.39E-06
miR-192*	54.77	112.38	0.49	1.01E-05
miR-767-5p	52.74	219.15	0.24	1.08E-05

[0285] To evaluate the predictive value of miRNA dysregulation on AMI, we calculated Receiver Operator Characteristic curves (ROC) for each of the best miRNAs together with the area under the curve value (AUC). For the most predictive single miRNA, miR-1291, we obtained an AUC value of 0.957. Using miR-1291 we classified 17 of the 20 disease samples and 26 of 29 controls correctly resulting in a specificity of 92.9% and a sensitivity of 85% with a test accuracy of 89.8% (see **Figure 3**).

MiR-30c, miR-145, and miR-223 levels significantly correlate with Troponin T levels

[0286] With the ability of single miRNAs to predict the presence of AMI, we next wondered if the magnitude of miRNA dysregulation correlates with infarct sizes estimated by Troponin T release (hsTnT). To this end, we computed for all significantly dysregulated miRNAs the correlation between miRNA expression and hsTnT at day 3 and 4. Furthermore, we calculated correlations to peak hsTnT levels. We identified in AMI three significantly upregulated miRNAs that show high correlation to Troponin T levels, with correlation coefficients up to 0.74. **Figure 4** represents the three miRNAs with highest correlation (linear) to Troponin T, miR-30c (A), miR-145 (B), and miR-223 (C) (see also **Table 2**).

Table 2: Correlation of miRNA levels and Troponin T release.

miRNA	Day 3			Peak		
	Correlation coefficient to hsTnT	Confidence intervall	p-value	Correlation coefficient ot hsTnT	Confidence intervall	p-value
miR-30c	0.667	0.31 - 0.86	0.0018	0.713	0.39-0.88	0.0004
miR-145	0.665	0.30-0.86	0.0019	0.710	0.39-0.88	0.0005
miR-223	0.667	0.32-0.87	0.0015	0.736	0.43-0.89	0.0002

Complex miRNA signatures discriminate AMI patients from controls

[0287] Although single miRNAs may predict the presence of AMI with good sensitivity and specificity, we tested whether complex miRNA signatures derived from unsupervised hierarchical clustering and supervised classification may improve the sensitivity and specificity.

[0288] To test for common signatures in AMI patients and controls, we applied hierarchical clustering of expression

levels of the 100 most significantly dysregulated miRNAs using the Euclidian distance measure. As shown in **Figure 5**, the algorithm correctly clusters all patients and controls separately, with only two outliers. Based on the ability to differentially cluster miRNA patterns in controls and AMI subjects and in order to improve the predictive power of a miRNA-based biomarker screening, we combined the information content of multiple miRNAs by using machine learning techniques. In detail, we applied Support Vector Machines (SVM) with different kernels as described in Materials and Methods. The best results were obtained using radial basis function SVM and a subset of 120 miRNAs. The cross validation procedure has been carried out 20 times to gain additional statistical significance. On average, the selected miRNAs allowed discrimination between blood samples of AMI patients and blood samples of controls with an accuracy of 95%, a specificity of 100%, and a sensitivity of 90% (**Figure 6A**). The AUC value for this signature is 0.983. In permutation tests significantly decreased accuracy, specificity, and sensitivity rates were computed, resembling random guessing. As shown in one randomly selected example of the classification algorithm, patients and controls can well be discriminated except for two outliers, leading to a specificity of 100%, a sensitivity of 90%, and a test accuracy of 95% (**Figure 6B**).

Conclusions

[0289] Today, biomarkers play a crucial role in the diagnosis of cardiovascular diseases such as acute myocardial infarction and heart failure. However, many of these markers have shortcomings such as reduced sensitivity, not sufficient specificity or do not allow timely diagnosis. A multiple biomarker strategy may circumvent these limitations by adding accuracy and predictive power. To evaluate for first time, if miRNA profiles could potentially serve as a new class of biomarkers, we assessed here whole-genome miRNA expression levels in peripheral blood from patients with acute myocardial infarction (AMI). We find that a unique miRNA signature predicts with high specificity, sensitivity, and accuracy AMI even at a stage where some patients are still Troponin T negative.

[0290] In recent studies miRNAs were identified as novel regulators and modifiers of cardiac development, function, and disease [21]. For instance, miRNA-21 controls cardiac fibrosis in response to cardiac overload via ERK-MAP-Kinase signaling [22]. Furthermore, miRNAs were found to be differentially regulated in various cardiac diseases such as ischemic heart disease, arrhythmias, and maladaptive hypertrophy, implicating that specific miRNA signatures might predict distinct disease states and serve as novel biomarkers [8, 9]. We find here that most miRNAs that are dysregulated in AMI patients are not heart-specific. However, this is not surprising, since our miRNA profiles are derived from peripheral blood cells and not myocardial tissue. Hence, miRNAs found to be dysregulated in AMI might equally be derived from other cellular population that play a role in AMI pathophysiology, such as endothelial cells involved in plaque rupture, thrombocytes in aggregation, but also inflammatory cells that are recruited to the ischemic area. Furthermore, miRNAs released from damaged tissue can be taken up by other cells, resulting in convergence of serum and cellular miRNAs [23]. Accordingly, next to the non-cardiac miRNAs we also found cardiac miRNAs such as miR-21, miR-30c, and miR-1 to be up-regulated in blood from AMI patients, implicating that these miRNAs may have been released from ischemic myocardium. Interestingly, in a candidate approach miRNA-1 levels were also found to be elevated in serum of AMI patients [24]. However, with this single biomarker approach, AMI patients could be distinguished from controls only with a moderate sensitivity and specificity (AUC = 0.774) [24]. By contrast, to increase the predictive power of miRNA-based diagnosis, we combined here whole-genome miRNA profiling with pattern-recognition algorithms leading to much higher sensitivity and specificity (AUC = 0.983) in the diagnosis of AMI.

[0291] Cardiac Troponins are currently the best validated biomarkers for the diagnosis of AMI. However, measurable amounts of Troponin proteins are usually not released from damaged myocardium before 4-8 hours after onset of symptoms, making an early biomarker-based diagnosis of AMI rather difficult. Accordingly, 45% of AMI patients included in this study were still Troponin-negative (TnT <50pg/ml) when entering the catheter laboratory and blood was drawn for miRNA analyses. However, miRNA profiles of these patients also showed the AMI characteristic signature, implicating that miRNA signatures might improve biomarker-based early diagnosis of AMI.

[0292] Next to their diagnostic potential, cardiac biomarkers can provide information on disease severity and prognosis [25, 26]. For instance, cardiac Troponin T levels directly correlate with the size of myocardial infarction [27, 28]. Accordingly, we found here that expression levels of three miRNAs, miR-30c, miR-145, and miR-223, significantly correlate with Troponin T levels in AMI patients. Interestingly, miR-30c and miR-233 are highly expressed in the heart and hence might be directly derived from damaged myocardium [29].

EXAMPLE: 2

Abstract

[0293] MicroRNAs (miRNAs) are important regulators of adaptive and maladaptive responses in cardiovascular diseases and hence are considered to be potential therapeutical targets. However, their role as novel biomarkers for the diagnosis of cardiovascular diseases still needs to be systematically evaluated. We assessed here for the first time

whole-genome miRNA expression in peripheral total blood samples of patients with acute myocardial infarction (AMI). We identified 121 miRNAs, which are significantly dysregulated in AMI patients in comparison to healthy controls. Amongst these, miR-1291 and miR-663b show the highest sensitivity and specificity for the discrimination of cases from controls. Using a novel self-learning pattern recognition algorithm, we identified a unique signature of 20 miRNAs that predicts AMI with even higher power (specificity = 96%, sensitivity = 90%, and accuracy = 93%). In addition, we show that miR-30c and miR-145 levels correlate with infarct sizes estimated by Troponin T release. The here presented study shows that both, single miRNAs and especially miRNA signatures derived from peripheral blood could be valuable novel biomarkers for cardiovascular diseases.

Introduction

[0294] MicroRNAs (miRNAs) represent a group of regulatory elements that enable cells to fine-tune complex gene expression cascades in a wide range of biological processes, such as proliferation, differentiation, apoptosis, and stress-response [38, 41, 55, 71, 72]. In the cardiovascular system, miRNAs are not only important for heart and vascular development, but also play an essential role in cardiac pathophysiology, such as hypertrophy, arrhythmia, and ischemia [36, 40]. However, their potential role as biomarkers for the diagnosis of cardiovascular diseases has not been systematically evaluated yet.

[0295] Today, biomarkers play a key role in early diagnosis, risk stratification, and therapeutic management of cardiac diseases such as acute myocardial infarction (AMI) and heart failure [51, 54, 57, 61]. Established biomarkers such as the cardiac troponins and b-type natriuretic peptides were mainly discovered by candidate approach [51, 60]. By contrast, the recent development of high-throughput molecular technologies that allow with a reasonable effort the analysis of whole transcriptomes, proteomes, and metabolomes of individuals at risk, may lead to the discovery of novel biomarkers in an unbiased approach [44, 45].

[0296] In the present study we aimed to identify a miRNA signature for the diagnosis of AMI, which is not solely based on the release of miRNAs from necrotic myocardium, but also on active processes involved in the pathogenesis of AMI, like inflammation, plaque rupture, and vascular injury. Therefore, we assessed for the first time the expression of miRNAs on a whole-genome level in total peripheral blood of patients with AMI and identified a unique miRNA signature that predicts myocardial infarction with high specificity and sensitivity, implicating that both, single miRNAs and complex miRNA signatures could be used as novel biomarkers for the diagnosis of cardiovascular diseases.

Materials and Methods

Study population

[0297] According to *a priori* power analyses (power of 0.95), we included 20 patients with acute ST Elevation Myocardial Infarction (STEMI) and 20 controls in the present study. Acute myocardial infarction (AMI) was diagnosed according to the ESC/AHA redefined guidelines. Vessel occlusion by an underlying thrombotic event as cause of AMI was confirmed in all patients by early coronary angiography. As control served miRNA profiles from 20 control subjects without acute coronary syndrome, who underwent routine coronary angiography (see **Table 3** for detailed clinical characteristics). MiRNA profiles from 20 healthy volunteers recruited during the "Biomarker Discovery Center" pilot study served as an internal control. The analysis of blood from patients and controls has been approved by local ethics committees and participants have given written informed consent. Serial Troponin T levels were assessed using the Elecsys highly sensitive Troponin T assay (Roche, Germany) [46].

MiRNA expression profiling from whole peripheral blood samples

[0298] 5 ml blood was collected from study subjects in PAXgene Blood RNA tubes (BD, USA) and stored at 4°C until total RNA was extracted from blood cells using the miRNeasy Mini Kit (Qiagen, Germany) [56]. MiRNA expression profiling was performed by personnel blinded to patient characteristics. Samples were analyzed with the Geniom Real-time Analyzer (febit, Germany) using the Geniom Biochip miRNA homo sapiens. Each array contains 7 replicates of 866 miRNAs and miRNA star sequences as annotated in the Sanger miRBase 12.0 [47]. Sample labelling with biotin was carried out by microfluidic-based enzymatic on-chip labelling of miRNAs (MPEA) as described before [68].

[0299] Following hybridization for 16 hours at 42°C the biochip was washed and signals were measured. The resulting images were evaluated using the Geniom Wizard Software (febit, Germany). For each array, the median signal intensity of all features was extracted from the raw data file such that for each miRNA seven intensity values were calculated corresponding to each replicate on the array. Following background correction, the seven replicate intensity values of each miRNA were summarized by their median value. To normalize the data across different arrays, quantile normalization was applied and all further analyses were carried out using the normalized and background subtracted intensity values.

To this end, we removed those miRNAs having an overall median signal intensity of less than 10. The final data set contained expression levels of 697 miRNAs.

[0300] To verify the accuracy of the microarray based miRNA measurements, expression levels of miR-145, -30c, -455-3p, -10b*, -216a, -1291, and -223 were assessed using quantitative real-time PCR (measured in triplets) according to manufacture's instructions (ABI, USA). As reference served the small nuclear RNA RNU6B-2.

Statistical analysis

[0301] After ensuring approximate normal distribution of the measured intensity values using Shapiro-Wilk test, we carried out parametric t-test and limma test (unpaired, two-tailed) for each miRNA separately to detect miRNAs with differential expression between the patient and control groups. The resulting p-values were adjusted for multiple testing by Benjamini-Hochberg equation [34]. Correlation coefficients between Troponin T and miRNA levels were calculated using Pearson's product-moment coefficient. Outlier testing was performed using the tests of Grubbs and Dixon. Clustering of miRNAs has been carried out using complete linkage hierarchical clustering. As distance measure, the Euclidian distance has been applied and miRNAs and samples have been clustered independently of each other. To assess significance of the clustering, Fishers exact test on the contingency table has been applied.

[0302] In addition to the single biomarker analysis, classification of samples using miRNA patterns was carried out using Support Vector Machines (SVM) as implemented in the R e1071 package (<http://www.r-project.org>) [64]. In particular, different kernel SVMs (linear, polynomial, sigmoid, radial basis function) were evaluated, where the cost parameter was sampled from 0.01 to 10 in decimal powers. The measured miRNA profiles were classified using 20 repetitions of standard 10-fold cross-validation. The classification has been carried out using equal class sizes. To detect the most suitable set of miRNAs that achieves the best discriminatory performance, a feature extraction (subset selection) method relying on t-test p-values was used. In detail, the following filter technique was applied: The s miRNAs with lowest p-values in the t-test were computed on the training set in each fold of the cross validation, where s was sampled from 1 to 697 in regular intervals. The respective subset was used to train the SVM and to carry out the prediction of the test samples. The mean accuracy, specificity, and sensitivity were calculated for each subset size. We additionally computed the area under the curve value (AUC), which is more discriminative than calculating the accuracy alone [33]. To check for overtraining we applied permutation tests. Here, we sampled the class labels randomly and carried out classifications using the permuted class labels. All statistical analyzes were performed using R.

Results

Acute ST Elevation Myocardial Infarction leads to dysregulation of specific miRNAs

[0303] In the present pilot study, we analyzed the expression of 866 miRNAs and miRNA star sequences in blood cells of 20 patients with acute myocardial infarction (AMI) and 20 control subjects. Mean age in AMI patients was 59.25 ± 14 years and in controls 63.30 ± 14.8 years ($p=0.38$). In the AMI group 4/20 and in the controls 6/20 patients were female ($p=0.72$). According to ECG criteria, 15 patients showed signs of inferior/posterior wall infarction and 5 of anterior wall infarction. The blood for miRNA and Troponin T measurements was drawn in the mean 3.0 ± 2.3 hours after the reported onset of symptoms. The mean hsTnT on admission was 345.8 ± 562.8 pg/ml. 10 patients (50%) with AMI had Troponin T levels of <50 pg/ml, and 3 of them were below 14pg/ml (15%). White blood cell counts showed no significant differences between both groups.

[0304] To test for the overall correlation of miRNA expression between cases and controls, we computed the median expression of all miRNAs in both groups on a logarithmic scale. As shown in the scatter plot in **Figure 22A**, both groups had high correlation of 0.891 and data variance as low as 0.002. To cross-validate the whole-genome miRNA microarray, we exemplarily measured the expression levels of up- and downregulated miRNAs by real-time PCR. We find a high reproducibility between both methods. Ensuring an approximate normal distribution using Shapiro-Wilk test, we performed two-tailed unpaired t-tests and limma test for each miRNA. The respective p-values were adjusted for multiple testing by the Benjamini-Hochberg approach [48]. In total, we detected 121 miRNAs to be significantly dysregulated in blood cells from AMI patients in comparison to controls at an adjusted significance level of $p<0.05$. Histogram plots of the logarithm of fold ratios, the raw t-test and limma p-values, and the adjusted p-values are presented in **Figure 22B**. Notably, from 121 dysregulated miRNAs only 45 (37%) were upregulated, while 76 (63%) were downregulated in AMI patients. The expression values of the 20 most significantly down- and upregulated miRNAs are shown in **Figure 23A and B**. Interestingly, miR-21, which is known to be upregulated in cardiomyocytes after myocardial infarction and heart failure, was significantly upregulated in blood of AMI patients in comparison to healthy volunteers, however was not significantly dysregulated in comparison to the control group.

[0305] To now evaluate the predictive value of dysregulated miRNA for AMI, we calculated Receiver Operator Characteristic curves (ROC) for each of the best miRNAs together with the area under the curve value (AUC). For the most

predictive miRNAs, miR-1291 and miR-663b, we obtained AUC values of up to 0.94 (**Figure 24A and B**). Using miR-1291, we classified 17 of the 20 disease samples and 17 of 20 controls correctly resulting in a specificity of 85% and a sensitivity of 85% with according test accuracy of 85%. miR-663b shows even better predictive values, allowing us to classify 19 of 20 cases and 18 of 20 controls correctly, resulting in specificity, sensitivity, and accuracy of 95%, 90%, and 92.5%, respectively.

MiR-145 and MiR-30c levels significantly correlate with Troponin T levels

[0306] With the ability of single miRNAs to predict AMI, we next wondered if the magnitude of miRNA dysregulation correlates with infarct sizes estimated by Troponin T release (hsTnT). To this end, we computed for all dysregulated miRNAs the correlation between miRNA expression and hsTnT at day 3 and 4. Furthermore, we calculated correlations to peak hsTnT levels. We identified two upregulated miRNAs in AMI patients that show high correlation to Troponin T levels, with correlation coefficients up to 0.71. **Figure 25** represents the two miRNAs with highest linear correlation to Troponin T, miR-145 (A, C) and miR-30c (B, C) (see also Table 4).

Table 3: Patient characteristics.

Characteristics	Patients with AMI (n=20)	Patients without AMI (n=20)	P
Age (years)	59.3 ± 14	63.3 ± 14.8	0.38
Male/female (n/n)	16/4	14/6	0.72
Current smoking, n (%)	6 (30)	4 (20)	0.72
DM, n (%)	3 (15)	4 (20)	1.00
Hypertension, n (%)	11 (55)	13 (65)	0.75
Hyperlipidaemia, n (%)	9 (45)	6 (30)	0.52
SBP (mmHg)	134 ± 27	128 ± 13	0.45
DBP (mmHg)	80 ± 15	73 ± 9	0.08
TG (mg/dL)	170.4 ± 49.9	139.4 ± 77.5	0.44
HDL (mg/dL)	38.1 ± 12.6	44.4 ± 28.3	0.65
LDL (mg/dL)	103.5 ± 38.9	104.2 ± 34.7	0.97
WBC (/nl)	10.28 ± 3.6	9.39 ± 3.2	0.47
Creatinine (mg/dL)	1.12 ± 0.68	0.98 ± 0.24	0.43
Urea (mg/dL)	39.2 ± 21.4	36.4 ± 10.1	0.62
DM = Diabetes mellitus, SBP = systolic blood pressure, DBP = diastolic blood pressure, TG = triglycerides, HDL = high-density lipoprotein, LDL = low-density lipoprotein, WBC = white blood cell count.			

Table 4: Correlation of miRNA levels and Troponin T release.

miRNA	Day 3			peak		
	Correlation coefficient to hsTnT	Confidence intervall	p-value	Correlation coefficient to hsTnT	Confidence intervall	p-value
miR-30c	0.667	0.31 - 0.86	0.0018	0.713	0.39-0.88	0.0004
miR-145	0.665	0.30-0.86	0.0019	0.710	0.39-0.88	0.0005
hsTnT = high sensitive Troponin T.						

MiRNA signatures enhance diagnostic discrimination of AMI patients from controls

[0307] Although single miRNAs may predict the presence of AMI with good sensitivity and specificity, we tested whether complex miRNA signatures derived from unsupervised hierarchical clustering and supervised classification may improve the sensitivity and specificity.

[0308] First, to test for common patterns in AMI patients and controls, we applied hierarchical clustering using the expression levels of the 20 miRNAs with highest data variance and applied the Euclidian distance measure. As shown in **Figure 26**, the algorithm clusters all patients and controls separately, with only three outliers. The significance of the clustering has been computed by Fishers test with a p-value of <0.001. Based on the ability to differentially cluster miRNA

patterns in controls and AMI subjects and in order to improve the predictive power of a miRNA-based biomarker, we next combined the information content of multiple miRNAs by using statistical learning techniques. In detail, we applied Support Vector Machines (SVM) with different kernels as described in Materials and Methods. The best results were obtained using radial basis function SVM and a subset of 20 miRNAs. The cross validation procedure has been carried out 20 times to gain additional statistical significance. As shown in **Figure 27A**, the values for sensitivity, specificity, and accuracy increased with the number of selected miRNAs in the diagnostic signature. 20 miRNAs allowed discrimination of AMI patients and controls with an accuracy of 93%, a specificity of 96%, and a sensitivity of 90%. The AUC for the AMI signature comprising 20 miRNAs (miR-142-5p, -498, -492, -1281, -497*, -151-5p, -802, -23b*, -455-3p, -1250, -380*, -135b*, -345, -566, -631, -1254, -139-5p, -892b, 20b*, and -146b-3p) is 0.99, representing a significant improvement to single miRNA markers (**Figure 27B**). As shown in the classification result, this signature allows discrimination of patients and controls except for three outliers (**Figure 27C**). In permutation tests significantly decreased accuracy, specificity, and sensitivity rates were computed, resembling random guessing.

Discussion

[0309] Today, biomarkers play a fundamental role in the diagnosis of cardiovascular diseases such as acute myocardial infarction and heart failure. However, many of these markers have shortcomings such as reduced sensitivity, not sufficient specificity or do not allow timely diagnosis. A multiple biomarker strategy may circumvent these limitations by adding accuracy and predictive power. To evaluate for the first time if complex miRNA signatures could potentially serve as a new class of biomarkers, we assessed here whole-genome miRNA expression levels in total peripheral blood from patients with acute myocardial infarction (AMI). We find that a unique miRNA signature predicts AMI even at a stage where some patients are still Troponin T negative.

[0310] In recent studies, miRNAs were identified as novel regulators and modifiers of cardiac development, function, and disease [58]. For instance, miRNA-21 not only controls cardiac fibrosis in response to cardiac overload, but also is upregulated in the myocardium during the early phase of infarction [40, 65]. We measured increased levels of miR-21 in AMI patients in comparison to healthy individuals, but not in comparison to our control cohort, which includes a high number of patients with stable coronary artery disease (CAD). Hence, the high levels of miR-21 in AMI patients might be due to the underlying CAD, which goes along with elevated miR-21 levels in circulating angiogenic progenitor cells [43]. Likewise, most miRNAs found to be dysregulated in AMI patients are not heart-specific. However, this is not surprising, since our miRNA profiles are derived from whole peripheral blood and not myocardial tissue. Hence, dysregulated miRNAs in AMI might equally be derived from other cellular population that play an active role in AMI pathophysiology, such as endothelial and smooth muscle cells involved in plaque rupture and vessel injury, thrombocytes in aggregation, and inflammatory cells that are recruited to the ischemic area. For instance, the vascular smooth muscle-enriched miR-145 is involved in neointima repair in response to vascular injury, regulating cytoskeletal components and migratory activity of smooth muscle cells (SMC) [70]. Thus, elevated miR-145 levels in the AMI group might be a result of vessel injury during plaque rupture. Similarly, miR-27b, which directly targets and destabilizes peroxisome proliferator activated receptor-gamma (PPAR γ) mRNA [50], is also upregulated in the AMI group (24.8 fold; $p < 0.05$). Consequently, elevated miR-27b might result in decreased PPAR γ expression in SMCs, enhancing their ability to proliferate, migrate and participate vascular remodeling processes [59]. Peripheral blood monocytes (PBMC) are critically involved in plaque destabilization and rupture as well as early inflammatory responses during myocardial infarction [35, 52]. MiR-134, which is strongly upregulated in our AMI cohort, was very recently identified as PBMC-based biomarker that is able to identify CAD patients at risk for acute coronary syndromes (ACS) [49]. Thus, studying the time-course of miR-134 in PBMCs might reveal its potential as a very early marker for ACS and AMI. In addition to miRNAs transcribed in peripheral blood cells, miRNAs released from damaged tissue can be taken up by leukocytes, resulting in the so-called convergence of serum and cellular miRNAs [37]. A recent study identified miRNAs specifically modulated in peripheral blood cells of heart failure patients. Intriguingly, many of the identified miRNAs were previously reported to be misexpressed in failing hearts of humans and mice [67]. Accordingly, next to the non-cardiac miRNAs, which significantly contribute to the AMI specific signature, we also found important, cardiac-enriched miRNAs such as miR-30c to be upregulated in blood from AMI patients, implicating that those might have been released from ischemic myocardium.

[0311] Cardiac Troponins are currently the best validated biomarkers for the diagnosis of AMI. However, measurable amounts of Troponin proteins are usually not released from damaged myocardium before 4 to 8 hours after onset of symptoms, making an early biomarker-based diagnosis of AMI rather difficult. Accordingly, 50% of AMI patients included in this study were still Troponin-negative (TnT $< 50\text{pg/ml}$) when entering the catheter laboratory and blood was drawn for miRNA analyses. However, miRNA profiles of these patients also showed the AMI characteristic signature, implicating that miRNA signatures might improve biomarker-based early diagnosis of myocardial infarction.

[0312] Next to their diagnostic potential, cardiac biomarkers can provide information on disease severity and prognosis [30, 62, 63]. For instance, cardiac Troponin T levels directly correlate with the size of myocardial infarction [53, 66]. Accordingly, we find that early expression levels of miR-30c and miR-145 significantly correlate with Troponin T levels.

Interestingly, miR-30c is highly expressed in the heart and hence might be directly derived from damaged myocardium [42].

[0313] In a recently published candidate approach, miRNA-1 levels were found to be elevated in serum of AMI patients [32]. However, with this single biomarker approach, AMI patients could be distinguished from controls with only a moderate sensitivity and specificity (AUC = 0.774), indicating that miRNA-1 might not be the optimal marker. In subsequent candidate studies using different cardiac miRNAs, such as miR-208a, -133b, and -499-5p, the predictive values were already considerably better [31, 39, 69]. To further increase the predictive power of miRNA-based markers, we combined here whole-genome miRNA profiling with pattern-recognition algorithms. As shown, our multi-marker approach might further increase sensitivity, specificity, and accuracy. However, the number of samples used in our analysis is too small to definitely proof the diagnostic power of microRNA signatures and their value for clinical testing of AMI patients. Hence, future prospective trials on large patient cohorts are needed to establish miRNAs as a novel biomarker class for acute myocardial infarction.

REFERENCES

[0314]

1. Zhao Y, Samal E, Srivastava D. Serum response factor regulates a muscle-specific microRNA that targets Hand2 during cardiogenesis. *Nature*. 2005;436:214-20.
2. Dresios J, Aschrafi A, Owens GC, Vanderklish PW, Edelman GM, Mauro VP. Cold stress-induced protein Rbm3 binds 60S ribosomal subunits, alters microRNA levels, and enhances global protein synthesis. *Proc Natl Acad Sci USA*. 2005;102:1865-70.
3. Xu P, Vernoooy SY, Guo M, Hay BA. The Drosophila microRNA Mir-14 suppresses cell death and is required for normal fat metabolism. *Curr Biol*. 2003;13 :790-5.
4. Cimmino A, Calin GA, Fabbri M, Iorio MV, Ferracin M, Shimizu M, Wojcik SE, Aqeilan RI, Zupo S, Dono M, Rassenti L, Alder H, Volinia S, Liu CG, Kipps TJ, Negrini M, Croce CM. miR-15 and miR-16 induce apoptosis by targeting BCL2. *Proc Natl Acad Sci U S A*. 2005;102:13944-9.
5. Calin GA, Garzon R, Cimmino A, Fabbri M, Croce CM. MicroRNAs and leukemias: how strong is the connection? *Leuk Res*. 2006;30:653-5.
6. Calin GA, Ferracin M, Cimmino A, Di Leva G, Shimizu M, Wojcik SE, Iorio MV, Visone R, Sever NI, Fabbri M, Iuliano R, Palumbo T, Pichiorri F, Roldo C, Garzon R, Sevignani C, Rassenti L, Alder H, Volinia S, Liu CG, Kipps TJ, Negrini M, Croce CM. A MicroRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. *N Engl J Med*. 2005;353:1793-801.
7. Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell*. 1993;75:843-54.
8. Dong S, Cheng Y, Yang J, Li J, Liu X, Wang X, Wang D, Krall TJ, Delphin ES, Zhang C. MicroRNA expression signature and the role of microRNA-21 in the early phase of acute myocardial infarction. *J Biol Chem*. 2009;284:29514-25.
9. Cai B, Pan Z, Lu Y. The Roles of MicroRNAs in Heart Diseases: A Novel Important Regulator. *Curr Med Chem*. 2009.
10. Newton PJ, Betihavas V, Macdonald P. The role of b-type natriuretic peptide in heart failure management. *Aust Crit Care*. 2009;22:117-23.
11. Lainscak M, Anker MS, von Haehling S, Anker SD. Biomarkers for chronic heart failure : diagnostic, prognostic, and therapeutic challenges. *Herz*. 2009;34:589-93.
12. Manzano-Fernandez S, Boronat-Garcia M, Albaladejo-Oton MD, Pastor P, Garrido IP, Pastor-Perez FJ, Martinez-Hernandez P, Valdes M, Pascual-Figal DA. Complementary prognostic value of cystatin C, N-terminal pro-B-type natriuretic Peptide and cardiac troponin T in patients with acute heart failure. *Am J Cardiol*. 2009;103:1753-9.
13. Katus HA, Remppis A, Looser S, Hallermeier K, Scheffold T, Kubler W. Enzyme linked immuno assay of cardiac troponin T for the detection of acute myocardial infarction in patients. *J Mol Cell Cardiol*. 1989;21:1349-53.
14. Mukoyama M, Nakao K, Saito Y, Ogawa Y, Hosoda K, Suga S, Shirakami G, Jougasaki M, Imura H. Increased human brain natriuretic peptide in congestive heart failure. *N Engl J Med*. 1990;323:757-8.
15. Gerszten RE, Wang TJ. The search for new cardiovascular biomarkers. *Nature*. 2008;451:949-52.
16. Gallego-Delgado J, Lazaro A, Osende JI, Barderas MG, Blanco-Colio LM, Duran MC, Martin-Ventura JL, Vivanco F, Egido J. Proteomic approach in the search of new cardiovascular biomarkers. *Kidney Int Suppl*. 2005:S103-7.
17. Giannitsis E, Roth HJ, Leithauser RM, Scherhag J, Beneke R, Katus HA. New highly sensitivity assay used to measure cardiac troponin T concentration changes during a continuous 216-km marathon. *Clin Chem*. 2009;55:590-2.
18. Griffiths-Jones S. miRBase: the microRNA sequence database. *Methods Mol Biol*. 2006;342:129-38.
19. Vorwerk S, Ganter K, Cheng Y, Hoheisel J, Stahler PF, Beier M. Microfluidic-based enzymatic on-chip labeling

of miRNAs. *N Biotechnol.* 2008;25:142-9.

20. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Statist Soc B.* 1995;57:289-300.

21. Meder B, Katus HA, Rottbauer W. Right into the heart of microRNA-133a. *Genes Dev.* 2008;22:3227-31.

22. Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, Galuppo P, Just S, Rottbauer W, Frantz S, Castoldi M, Soutschek J, Koteliensky V, Rosenwald A, Basson MA, Licht JD, Pena JT, Rouhanifard SH, Muckenthaler MU, Tuschl T, Martin GR, Bauersachs J, Engelhardt S. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. *Nature.* 2008;456:980-4.

23. Chen X, Ba Y, Ma L, Cai X, Yin Y, Wang K, Guo J, Zhang Y, Chen J, Guo X, Li Q, Li X, Wang W, Wang J, Jiang X, Xiang Y, Xu C, Zheng P, Zhang J, Li R, Zhang H, Shang X, Gong T, Ning G, Zen K, Zhang CY. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. *Cell Res.* 2008;18:997-1006.

24. Ai J, Zhang R, Li Y, Pu J, Lu Y, Jiao J, Li K, Yu B, Li Z, Wang R, Wang L, Li Q, Wang N, Shan H, Yang B. Circulating microRNA-1 as a potential novel biomarker for acute myocardial infarction. *Biochem Biophys Res Commun.* 2009.

25. Risk stratification and survival after myocardial infarction. *N Engl J Med.* 1983;309:331-6.

26. Rottbauer W, Greten T, Muller-Bardorff M, Remppis A, Zehelein J, Grunig E, Katus HA. Troponin T: a diagnostic marker for myocardial infarction and minor cardiac cell damage. *Eur Heart J.* 1996;17 Suppl F:3-8.

27. Kurz K, Schild C, Isfort P, Katus HA, Giannitsis E. Serial and single time-point measurements of cardiac troponin T for prediction of clinical outcomes in patients with acute ST-segment elevation myocardial infarction. *Clin Res Cardiol.* 2009;98:94-100.

28. Tzivoni D, Koukoui D, Guetta V, Novack L, Cowing G. Comparison of Troponin T to creatine kinase and to radionuclide cardiac imaging infarct size in patients with ST-elevation myocardial infarction undergoing primary angioplasty. *Am J Cardiol.* 2008;101:753-7.

29. Duisters RF, Tijssen AJ, Schroen B, Leenders JJ, Lentink V, van der Made I, Herias V, van Leeuwen RE, Schellings MW, Barenbrug P, Maessen JG, Heymans S, Pinto YM, Creemers EE. miR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. *Circ Res.* 2009;104:170-8, 6p following 178.

30. (1983) Risk stratification and survival after myocardial infarction. *N Engl J Med* 309:331-336

31. Adachi T, Nakanishi M, Otsuka Y, Nishimura K, Hirokawa G, Goto Y, Nonogi H, Iwai N (2010) Plasma microRNA 499 as a biomarker of acute myocardial infarction. *Clin Chem* 56:1183-1185

32. Ai J, Zhang R, Li Y, Pu J, Lu Y, Jiao J, Li K, Yu B, Li Z, Wang R, Wang L, Li Q, Wang N, Shan H, Yang B (2010) Circulating microRNA-1 as a potential novel biomarker for acute myocardial infarction. *Biochem Biophys Res Commun* 391:73-77

33. Aliferis CF, Statnikov A, Tsamardinos I, Schildcrout JS, Shepherd BE, Harrell FE, Jr. (2009) Factors influencing the statistical power of complex data analysis protocols for molecular signature development from microarray data. *PLoS ONE* 4:e4922

34. Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Statist Soc B* 57:289-300

35. Bose D, von Birgelen C, Zhou XY, Schmermund A, Philipp S, Sack S, Konorza T, Mohlenkamp S, Leineweber K, Kleinbongard P, Wijns W, Heusch G, Erbel R (2008) Impact of atherosclerotic plaque composition on coronary microembolization during percutaneous coronary interventions. *Basic Res Cardiol* 103:587-597

36. Cai B, Pan Z, Lu Y (2010) The roles of microRNAs in heart diseases: a novel important regulator. *Curr Med Chem* 17:407-411

37. Chen X, Ba Y, Ma L, Cai X, Yin Y, Wang K, Guo J, Zhang Y, Chen J, Guo X, Li Q, Li X, Wang W, Wang J, Jiang X, Xiang Y, Xu C, Zheng P, Zhang J, Li R, Zhang H, Shang X, Gong T, Ning G, Zen K, Zhang CY (2008) Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. *Cell Res* 18:997-1006

38. Cimmino A, Calin GA, Fabbri M, Iorio MV, Ferracin M, Shimizu M, Wojcik SE, Aqeilan RI, Zupo S, Dono M, Rassenti L, Alder H, Volinia S, Liu CG, Kipps TJ, Negrini M, Croce CM (2005) miR-15 and miR-16 induce apoptosis by targeting BCL2. *Proc Natl Acad Sci U S A* 102:13944-13949

39. D'Alessandra Y, Devanna P, Limana F, Straino S, Di Carlo A, Brambilla PG, Rubino M, Carena MC, Spazzafumo L, De Simone M, Micheli B, Biglioli P, Achilli F, Martelli F, Maggiolini S, Marenzi G, Pompilio G, Capogrossi MC (2010) Circulating microRNAs are new and sensitive biomarkers of myocardial infarction. *Eur Heart J* published online June 9, 2010 doi:10.1093/eurheartj/ehq167

40. Dong S, Cheng Y, Yang J, Li J, Liu X, Wang X, Wang D, Krall TJ, Delphin ES, Zhang C (2009) MicroRNA expression signature and the role of microRNA-21 in the early phase of acute myocardial infarction. *J Biol Chem* 284:29514-29525

41. Dresios J, Aschrafi A, Owens GC, Vanderklish PW, Edelman GM, Mauro VP (2005) Cold stress-induced protein Rbm3 binds 60S ribosomal subunits, alters microRNA levels, and enhances global protein synthesis. *Proc Natl Acad Sci USA* 102:1865-1870
42. Duisters RF, Tijssen AJ, Schroen B, Leenders JJ, Lentink V, van der Made I, Herias V, van Leeuwen RE, Schellings MW, Barenbrug P, Maessen JG, Heymans S, Pinto YM, Creemers EE (2009) miR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. *Circ Res* 104:170-178, 176p following 178
43. Fleissner F, Jazbutyte V, Fiedler J, Gupta SK, Yin X, Xu Q, Galuppo P, Kneitz S, Mayr M, Ertl G, Bauersachs J, Thum T (2010) Short communication: asymmetric dimethylarginine impairs angiogenic progenitor cell function in patients with coronary artery disease through a microRNA-21-dependent mechanism. *Circ Res* 107:138-143
44. Gallego-Delgado J, Lazaro A, Osende JI, Barderas MG, Blanco-Colio LM, Duran MC, Martin-Ventura JL, Vivanco F, Egido J (2005) Proteomic approach in the search of new cardiovascular biomarkers. *Kidney Int Suppl*:S103-107
45. Gerszten RE, Wang TJ (2008) The search for new cardiovascular biomarkers. *Nature* 451:949-952
46. Giannitsis E, Roth HJ, Leithauser RM, Scherhag J, Beneke R, Katus HA (2009) New highly sensitivity assay used to measure cardiac troponin T concentration changes during a continuous 216-km marathon. *Clin Chem* 55:590-592
47. Griffiths-Jones S (2006) miRBase: the microRNA sequence database. *Methods Mol Biol* 342:129-138
48. Hochberg Y (1988) A sharper bonferroni procedure for multiple tests of significance. *Biometrika* 75:185-193
49. Hoekstra M, van der Lans CA, Halvorsen B, Gullestad L, Kuiper J, Aukrust P, van Berkel TJ, Biessen EA (2010) The peripheral blood mononuclear cell microRNA signature of coronary artery disease. *Biochem Biophys Res Commun* 394:792-797
50. Jennewein C, von Knethen A, Schmid T, Brune B (2010) MicroRNA-27b contributes to lipopolysaccharide-mediated peroxisome proliferator-activated receptor gamma (PPARgamma) mRNA destabilization. *J Biol Chem* 285:11846-11853
51. Katus HA, Remppis A, Looser S, Hallermeier K, Scheffold T, Kubler W (1989) Enzyme linked immuno assay of cardiac troponin T for the detection of acute myocardial infarction in patients. *J Mol Cell Cardiol* 21:1349-1353
52. Konstantin MH, Aksoy H, Wabnitz GH, Volz C, Erbel C, Kirchgessner H, Giannitsis E, Katus HA, Samstag Y, Dengler TJ (2009) Beta2-integrin activation on T cell subsets is an independent prognostic factor in unstable angina pectoris. *Basic Res Cardiol* 104:341-351
53. Kurz K, Schild C, Isfort P, Katus HA, Giannitsis E (2009) Serial and single time-point measurements of cardiac troponin T for prediction of clinical outcomes in patients with acute ST-segment elevation myocardial infarction. *Clin Res Cardiol* 98:94-100
54. Lainscak M, Anker MS, von Haehling S, Anker SD (2009) Biomarkers for chronic heart failure : diagnostic, prognostic, and therapeutic challenges. *Herz* 34:589-593
55. Lee RC, Feinbaum RL, Ambros V (1993) The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell* 75:843-854
56. Leidinger P, Keller A, Borries A, Reichrath J, Rass K, Jager SU, Lenhof HP, Meese E (2010) High-throughput miRNA profiling of human melanoma blood samples. *BMC Cancer* 10:262
57. Manzano-Fernandez S, Boronat-Garcia M, Albaladejo-Oton MD, Pastor P, Garrido IP, Pastor-Perez FJ, Martinez-Hernandez P, Valdes M, Pascual-Figal DA (2009) Complementary prognostic value of cystatin C, N-terminal pro-B-type natriuretic Peptide and cardiac troponin T in patients with acute heart failure. *Am J Cardiol* 103:1753-1759
58. Meder B, Katus HA, Rottbauer W (2008) Right into the heart of microRNA-133a. *Genes Dev* 22:3227-3231
59. Meredith D, Panchatcharam M, Miriyala S, Tsai YS, Morris AJ, Maeda N, Stouffer GA, Smyth SS (2009) Dominant-negative loss of PPARgamma function enhances smooth muscle cell proliferation, migration, and vascular remodeling. *Arterioscler Thromb Vasc Biol* 29:465-471
60. Mukoyama M, Nakao K, Saito Y, Ogawa Y, Hosoda K, Suga S, Shirakami G, Jougasaki M, Imura H (1990) Increased human brain natriuretic peptide in congestive heart failure. *N Engl J Med* 323:757-758
61. Newton PJ, Betihavas V, Macdonald P (2009) The role of b-type natriuretic peptide in heart failure management. *Aust Crit Care* 22:117-123
62. Porela P, Pulkki K, Voipio-Pulkki LM, Pettersson K, Leppanen V, Nevalainen TJ (2000) Level of circulating phospholipase A2 in prediction of the prognosis of patients with suspected myocardial infarction. *Basic Res Cardiol* 95:413-417
63. Rottbauer W, Greten T, Muller-Bardorff M, Remppis A, Zehelein J, Grunig E, Katus HA (1996) Troponin T: a diagnostic marker for myocardial infarction and minor cardiac cell damage. *Eur Heart J* 17 Suppl F:3-8
64. Team-RDC (2008) R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria
65. Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, Galuppo P, Just S, Rottbauer W, Frantz S, Castoldi M, Soutschek J, Kotliansky V, Rosenwald A, Basson MA, Licht JD, Pena JT, Rouhanifard SH, Muckenthaler MU,

Tuschl T, Martin GR, Bauersachs J, Engelhardt S (2008) MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. *Nature* 456:980-984

66. Tzivoni D, Koukoui D, Guetta V, Novack L, Cowing G (2008) Comparison of Troponin T to creatine kinase and to radionuclide cardiac imaging infarct size in patients with ST-elevation myocardial infarction undergoing primary angioplasty. *Am J Cardiol* 101:753-757

67. Voellenkle C, van Rooij J, Cappuzzello C, Greco S, Arcelli D, Di Vito L, Melillo G, Rigolini R, Costa E, Crea F, Capogrossi MC, Napolitano M, Martelli F (2010) MicroRNA signatures in peripheral blood mononuclear cells of chronic heart failure patients. *Physiol Genomics* 42:420-426

68. Vorwerk S, Ganter K, Cheng Y, Hoheisel J, Stahler PF, Beier M (2008) Microfluidic-based enzymatic on-chip labeling of miRNAs. *N Biotechnol* 25:142-149

69. Wang GK, Zhu JQ, Zhang JT, Li Q, Li Y, He J, Qin YW, Jing Q (2010) Circulating microRNA: a novel potential biomarker for early diagnosis of acute myocardial infarction in humans. *Eur Heart J* 31:659-666

70. Xin M, Small EM, Sutherland LB, Qi X, McAnally J, Plato CF, Richardson JA, Bassel-Duby R, Olson EN (2009) MicroRNAs miR-143 and miR-145 modulate cytoskeletal dynamics and responsiveness of smooth muscle cells to injury. *Genes Dev* 23:2166-2178

71. Xu P, Vernooij SY, Guo M, Hay BA (2003) The Drosophila microRNA Mir-14 suppresses cell death and is required for normal fat metabolism. *Curr Biol* 13:790-795

72. Zhao Y, Samal E, Srivastava D (2005) Serum response factor regulates a muscle-specific microRNA that targets Hand2 during cardiogenesis. *Nature* 436:214-220

SEQUENCE LISTING

<110> Comprehensive Biomarker Center GmbH
 5 <120> Complex miRNA sets as novel biomarkers for an acute coronary syndrome
 <130> 505-17 EPT1
 10 <150> EP 10 004 190.4
 <151> 2010-04-20
 <150> US 61/326,043
 <151> 2010-04-20
 15 <150> EP 10 185 136.8
 <151> 2010-10-01
 <160> 283
 20 <170> PatentIn version 3.5
 <210> 1
 <211> 24
 <212> RNA
 <213> Homo sapiens
 25 <400> 1
 uggcccugac ugaagaccag cagu 24
 <210> 2
 30 <211> 22
 <212> RNA
 <213> Homo sapiens
 <400> 2
 35 ucuacaaagg aaagcgcuuu cu 22
 <210> 3
 <211> 24
 <212> RNA
 40 <213> Homo sapiens
 <400> 3
 agccugauua aacacaugcu cuga 24
 45 <210> 4
 <211> 21
 <212> RNA
 <213> Homo sapiens
 50 <400> 4
 aagugaucua aaggccuaca u 21
 55 <210> 5
 <211> 22
 <212> RNA
 <213> Homo sapiens

	<400> 5 auaagacgaa caaaagguu gu	22
5	<210> 6 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 6 uacccagagc augcagugug aa	22
15	<210> 7 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 7 uaguacugug cauaucucu au	22
25	<210> 8 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 8 uagcaaaaac ugcaguuacu uu	22
35	<210> 9 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 9 uuuuaacuc uaaugggaga ga	22
45	<210> 10 <211> 22 <212> RNA <213> Homo sapiens	
50	<400> 10 aggcaugac uucucacuag cu	22
55	<210> 11 <211> 26 <212> RNA <213> Homo sapiens	
	<400> 11 gugagggcgu gcaggccugg augggg	26
	<210> 12 <211> 21 <212> RNA <213> Homo sapiens	

	<400> 12	
	ucacagugaa ccggucucuu u	21
5	<210> 13	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
10	<400> 13	
	uauacaaggg cagacucucu cu	22
15	<210> 14	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
20	<400> 14	
	uggugggcac agaaucugga cu	22
25	<210> 15	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
30	<400> 15	
	cacuggcucc uuucugggua ga	22
35	<210> 16	
	<211> 21	
	<212> RNA	
	<213> Homo sapiens	
40	<400> 16	
	gcaguccaug ggcauauaca c	21
45	<210> 17	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
50	<400> 17	
	ugcuaugcca acauauugcc au	22
55	<210> 18	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
60	<400> 18	
	cugccaauuc cauaggucac ag	22
65	<210> 19	
	<211> 23	
	<212> RNA	
	<213> Homo sapiens	

	<400> 19	
	ugcaccaugg uugucugagc aug	23
5	<210> 20	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
10	<400> 20	
	acugcugagc uagcacuucc cg	22
15	<210> 21	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
20	<400> 21	
	cuccuacaua uuagcauuaa ca	22
25	<210> 22	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
30	<400> 22	
	acuguaguau gggcacuucc ag	22
35	<210> 23	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
40	<400> 23	
	cuuaugcaag auucccuucu ac	22
45	<210> 24	
	<211> 23	
	<212> RNA	
	<213> Homo sapiens	
50	<400> 24	
	gcaaagcaca cggccugcag aga	23
55	<210> 25	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
60	<400> 25	
	ugagaacuga auuccauagg cu	22
65	<210> 26	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	

	<400> 26	
	gaugagcuca uuguauaug ag	22
5	<210> 27	
	<211> 23	
	<212> RNA	
	<213> Homo sapiens	
10	<400> 27	
	ugaggggcag agagcgagac uuu	23
15	<210> 28	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
20	<400> 28	
	acagauucga uucuagggga au	22
25	<210> 29	
	<211> 21	
	<212> RNA	
	<213> Homo sapiens	
30	<400> 29	
	gugcauugua guugcauugc a	21
35	<210> 30	
	<211> 23	
	<212> RNA	
	<213> Homo sapiens	
40	<400> 30	
	uacuccagag ggcgucacuc aug	23
45	<210> 31	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
50	<400> 31	
	ucuacagugc acgugucucc ag	22
55	<210> 32	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
	<400> 32	
	ugguugacca uagaacaugc gc	22
	<210> 33	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	

	<400> 33 aaucaugugc agugccaaua ug	22
5	<210> 34 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 34 gaaagcgcuu cccuuugcug ga	22
15	<210> 35 <211> 21 <212> RNA <213> Homo sapiens	
20	<400> 35 cucccacaug caggguuugc a	21
25	<210> 36 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 36 acugcauuau gagcacuuaa ag	22
35	<210> 37 <211> 20 <212> RNA <213> Homo sapiens	
40	<400> 37 cuacaaaggg aagcccuuuc	20
45	<210> 38 <211> 22 <212> RNA <213> Homo sapiens	
50	<400> 38 caucaucguc ucaaaugagu cu	22
55	<210> 39 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 39 uaaucucagc uggcaacugu ga	22
	<210> 40 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 40	
	ccucccacac ccaaggcuug ca	22
5	<210> 41	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
10	<400> 41	
	uggugggcccg cagaacaugu gc	22
15	<210> 42	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
20	<400> 42	
	cuauacaauc uauugccuuc cc	22
25	<210> 43	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
30	<400> 43	
	ggauuccugg aaauacuguu cu	22
35	<210> 44	
	<211> 23	
	<212> RNA	
	<213> Homo sapiens	
40	<400> 44	
	ucucacacag aaaucgcacc cgu	23
45	<210> 45	
	<211> 21	
	<212> RNA	
	<213> Homo sapiens	
50	<400> 45	
	cccagauaa uggcacucuca a	21
55	<210> 46	
	<211> 21	
	<212> RNA	
	<213> Homo sapiens	
	<400> 46	
	uacugcagac aguggcaauc a	21
	<210> 47	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	

	<400> 47	
	cucuagaggg aagcgcuuc ug	22
5	<210> 48	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
10	<400> 48	
	uucacaagga ggugucauu au	22
15	<210> 49	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
20	<400> 49	
	ugucuacuc ccucaggcac au	22
25	<210> 50	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
30	<400> 50	
	cggcaacaag aaacugccug ag	22
35	<210> 51	
	<211> 27	
	<212> RNA	
	<213> Homo sapiens	
40	<400> 51	
	auugaucauc gacacuucga acgcaau	27
45	<210> 52	
	<211> 23	
	<212> RNA	
	<213> Homo sapiens	
50	<400> 52	
	caguaacaaa gauucauccu ugu	23
55	<210> 53	
	<211> 26	
	<212> RNA	
	<213> Homo sapiens	
60	<400> 53	
	gaugaugaug gcagcaaaau cugaaa	26
65	<210> 54	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	

	<400> 54 acacagggcu guugugaaga cu	22
5	<210> 55 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 55 cuuucagucg gauguuaca gc	22
15	<210> 56 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 56 uauugugccuu uggacuacau cg	22
25	<210> 57 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 57 ugccuacuga gcugaaacac ag	22
35	<210> 58 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 58 aaccaucgac cguugagugg ac	22
45	<210> 59 <211> 24 <212> RNA <213> Homo sapiens	
50	<400> 59 uugcagcugc cugggaguga cuuc	24
55	<210> 60 <211> 21 <212> RNA <213> Homo sapiens	
	<400> 60 uugggacaua cuuauqcuaa a	21
	<210> 61 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 61 ugugcgcagg gagaccucuc cc	22
5	<210> 62 <211> 17 <212> RNA <213> Homo sapiens	
10	<400> 62 ucgccuccuc cucuccc	17
15	<210> 63 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 63 acccgucccg uucgucccg ga	22
25	<210> 64 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 64 aaggagcuca cagucuauug ag	22
35	<210> 65 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 65 uggugguua caaaguaau ca	22
45	<210> 66 <211> 21 <212> RNA <213> Homo sapiens	
50	<400> 66 uuaggccgca gaucugggug a	21
55	<210> 67 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 67 caagcuugua ucuauaggua ug	22
	<210> 68 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 68 uggguuccug gcaugcugau uu	22
5	<210> 69 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 69 ugccuacuga gcugauauca gu	22
15	<210> 70 <211> 21 <212> RNA <213> Homo sapiens	
20	<400> 70 acggugcugg auguggccuu u	21
25	<210> 71 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 71 uguaaaacauc cuugacugga ag	22
35	<210> 72 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 72 aaaucucugc aggcaaaugu ga	22
45	<210> 73 <211> 21 <212> RNA <213> Homo sapiens	
50	<400> 73 cuccguuugc cuguuucgcu g	21
55	<210> 74 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 74 ccaaaacugc aguuacuuuu gc	22
	<210> 75 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 75 uuagggcccu ggcuccaucu cc	22
5	<210> 76 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 76 ucuucucugu uuuggccaug ug	22
15	<210> 77 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 77 caaucagcaa guauacugcc cu	22
25	<210> 78 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 78 cucuagaggg aagcgcuuuc ug	22
35	<210> 79 <211> 20 <212> RNA <213> Homo sapiens	
40	<400> 79 agagucuugu gaugucuugc	20
45	<210> 80 <211> 22 <212> RNA <213> Homo sapiens	
50	<400> 80 cucuagaggg aagcgcuuuc ug	22
55	<210> 81 <211> 19 <212> RNA <213> Homo sapiens	
	<400> 81 uggauuuuug gaucagggga	19
	<210> 82 <211> 17 <212> RNA <213> Homo sapiens	

	<400> 82 ucccuguucg ggcgcca	17
5	<210> 83 <211> 23 <212> RNA <213> Homo sapiens	
10	<400> 83 uucucgagga aagaagcacu uuc	23
15	<210> 84 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 84 uuuagagacg gggucuugcu cu	22
25	<210> 85 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 85 cagugguuuu acccuauggu ag	22
35	<210> 86 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 86 augguuccgu caagcaccau gg	22
45	<210> 87 <211> 22 <212> RNA <213> Homo sapiens	
50	<400> 87 cuuggcaccu agcaagcacu ca	22
55	<210> 88 <211> 21 <212> RNA <213> Homo sapiens	
	<400> 88 uacuuggaaa ggcaucaguu g	21
	<210> 89 <211> 21 <212> RNA <213> Homo sapiens	

	<400> 89	
	ugauauguuu gauauugggu u	21
5	<210> 90	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
10	<400> 90	
	ugcccuuaaa ggugaaccca gu	22
15	<210> 91	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
20	<400> 91	
	cugcaaugua agcacuucuu ac	22
25	<210> 92	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
30	<400> 92	
	cugggagagg guuguuuacu cc	22
35	<210> 93	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
40	<400> 93	
	ugcaacgaac cugagccacu ga	22
45	<210> 94	
	<211> 23	
	<212> RNA	
	<213> Homo sapiens	
50	<400> 94	
	ccucagggcu guagaacagg gcu	23
55	<210> 95	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
60	<400> 95	
	auguagggcu aaaagccaug gg	22
65	<210> 96	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	

	<400> 96 cguguauuuug acaagcugag uu	22
5	<210> 97 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 97 cugaagcuca gagggcucug au	22
15	<210> 98 <211> 21 <212> RNA <213> Homo sapiens	
20	<400> 98 aguuaggauu aggucgugga a	21
25	<210> 99 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 99 cugcgcaagc uacugccuug cu	22
35	<210> 100 <211> 20 <212> RNA <213> Homo sapiens	
40	<400> 100 uaaggcacgc ggugaauGCC	20
45	<210> 101 <211> 23 <212> RNA <213> Homo sapiens	
50	<400> 101 gcagcagaga auaggacuac guc	23
55	<210> 102 <211> 23 <212> RNA <213> Homo sapiens	
	<400> 102 uagugcaua uugcuuauag ggu	23
	<210> 103 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 103 ugucuacuac uggagacacu gg	22
5	<210> 104 <211> 23 <212> RNA <213> Homo sapiens	
10	<400> 104 ucccuguccu ccaggagcuc acg	23
15	<210> 105 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 105 uuuugcaaua uguuccugaa ua	22
25	<210> 106 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 106 acucaaaacc cuucagugac uu	22
35	<210> 107 <211> 25 <212> RNA <213> Homo sapiens	
40	<400> 107 aggcaccagc caggcauugc ucagc	25
45	<210> 108 <211> 22 <212> RNA <213> Homo sapiens	
50	<400> 108 aaaagcuggg uugagagggc ga	22
55	<210> 109 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 109 uauquaacau gguccacuaa cu	22
	<210> 110 <211> 23 <212> RNA <213> Homo sapiens	

	<400> 110 cuggagauau ggaagagcug ugu	23
5	<210> 111 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 111 auauuaccu uagcucaucu uu	22
15	<210> 112 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 112 acugcaguga aggcacuugu ag	22
25	<210> 113 <211> 23 <212> RNA <213> Homo sapiens	
30	<400> 113 uaggcagugu cauugcuga uug	23
35	<210> 114 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 114 accuugccuu gcugcccggg cc	22
45	<210> 115 <211> 22 <212> RNA <213> Homo sapiens	
50	<400> 115 uacugcagac guggcaauca ug	22
55	<210> 116 <211> 23 <212> RNA <213> Homo sapiens	
	<400> 116 ugagcgccuc gacgacagag ccg	23
	<210> 117 <211> 19 <212> RNA <213> Homo sapiens	

	<400> 117 aaaagcuggg uugagagga	19
5	<210> 118 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 118 uccgucucag uuacuuuaua gc	22
15	<210> 119 <211> 21 <212> RNA <213> Homo sapiens	
20	<400> 119 caaaacguga ggcgcugcua u	21
25	<210> 120 <211> 21 <212> RNA <213> Homo sapiens	
30	<400> 120 ucguggccug guccuccauua u	21
35	<210> 121 <211> 18 <212> RNA <213> Homo sapiens	
40	<400> 121 ugcuuccuuu cagagggg	18
45	<210> 122 <211> 22 <212> RNA <213> Homo sapiens	
50	<400> 122 augcaccugg gcaaggauuc ug	22
55	<210> 123 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 123 ugcccugugg acucaguucu gg	22
	<210> 124 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 124 acaguagucu gcacauuggu ua	22
5	<210> 125 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 125 ucugggcaac aaagugagac cu	22
15	<210> 126 <211> 20 <212> RNA <213> Homo sapiens	
20	<400> 126 acucaaacug ugggggcacu	20
25	<210> 127 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 127 cacgcucaug cacacacca ca	22
35	<210> 128 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 128 augggugaau uuguagaagg au	22
45	<210> 129 <211> 22 <212> RNA <213> Homo sapiens	
50	<400> 129 aaaaccgucu aguuacaguu gu	22
55	<210> 130 <211> 24 <212> RNA <213> Homo sapiens	
	<400> 130 agcagaagca gggagguucu ccca	24
	<210> 131 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 131 uaacugguug aacaacugaa cc	22
5	<210> 132 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 132 cugguuucac augguggcuu ag	22
15	<210> 133 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 133 caaaacuggc aauuacuuuu gc	22
25	<210> 134 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 134 uauquaacac gguccacuaa cc	22
35	<210> 135 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 135 caacaaauca cagucugcca ua	22
45	<210> 136 <211> 22 <212> RNA <213> Homo sapiens	
50	<400> 136 aaagugcuuc ccuuuggacu gu	22
55	<210> 137 <211> 20 <212> RNA <213> Homo sapiens	
	<400> 137 ggggagcugu ggaagcagua	20
	<210> 138 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 138 aacgccauua ucacacuaaa ua	22
5	<210> 139 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 139 uccgagccug ggucuccuc uu	22
15	<210> 140 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 140 ugcggggcua gggcuaacag ca	22
25	<210> 141 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 141 uauaccucag uuuuauacag ug	22
35	<210> 142 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 142 accuaucaa uauugucucu gc	22
45	<210> 143 <211> 21 <212> RNA <213> Homo sapiens	
50	<400> 143 caucccuugc augguggagg g	21
55	<210> 144 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 144 aguucuucag uggcaagcuu ua	22
	<210> 145 <211> 24 <212> RNA <213> Homo sapiens	

	<400> 145 ucccugagac ccuuuaaccu guga	24
5	<210> 146 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 146 cuauacaguc uacugucuuu cc	22
15	<210> 147 <211> 21 <212> RNA <213> Homo sapiens	
20	<400> 147 ucacuccucu ccucccgucu u	21
25	<210> 148 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 148 uuugaggcua cagugagauug ug	22
35	<210> 149 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 149 ucaguaaaug uuuauuagau ga	22
45	<210> 150 <211> 24 <212> RNA <213> Homo sapiens	
50	<400> 150 agccuggaag cuggagccug cagu	24
55	<210> 151 <211> 23 <212> RNA <213> Homo sapiens	
	<400> 151 agguugggau cgguugcaau gcu	23
	<210> 152 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 152 cuguugccac uaaccucaac cu	22
5	<210> 153 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 153 cucuagaggg aagcacuuuc ug	22
15	<210> 154 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 154 uucaaguaau ccaggauagg cu	22
25	<210> 155 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 155 ucaggcucag uccccucccg au	22
30	<210> 156 <211> 23 <212> RNA <213> Homo sapiens	
35	<400> 156 uacugcauca ggaacugauu gga	23
40	<210> 157 <211> 19 <212> RNA <213> Homo sapiens	
	<400> 157 gggcgccugu gaucccaac	19
45	<210> 158 <211> 24 <212> RNA <213> Homo sapiens	
50	<400> 158 uucuccaaaa gaaagcacuu ucug	24
55	<210> 159 <211> 21 <212> RNA <213> Homo sapiens	

	<400> 159 cauuauuacu uuugguacgc g	21
5	<210> 160 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 160 uaacacuguc ugguaacgau gu	22
15	<210> 161 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 161 acuuuaacau ggaagugcuu uc	22
25	<210> 162 <211> 21 <212> RNA <213> Homo sapiens	
30	<400> 162 cauaaaguag aaagcacuac u	21
35	<210> 163 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 163 uucuccaaaa gggagcacuu uc	22
45	<210> 164 <211> 23 <212> RNA <213> Homo sapiens	
50	<400> 164 cacucagccu ugagggcacu uuc	23
55	<210> 165 <211> 21 <212> RNA <213> Homo sapiens	
	<400> 165 uacaguacug ugauaacuga a	21
	<210> 166 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 166 gugacaucac auauacggca gc	22
5	<210> 167 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 167 gugagucucu aagaaaagag ga	22
15	<210> 168 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 168 ugagguagua guuuguacag uu	22
25	<210> 169 <211> 20 <212> RNA <213> Homo sapiens	
30	<400> 169 acugccccag gugcugcugg	20
35	<210> 170 <211> 20 <212> RNA <213> Homo sapiens	
40	<400> 170 augauaaaau guauacacac	20
45	<210> 171 <211> 19 <212> RNA <213> Homo sapiens	
50	<400> 171 aagcagcugc cucugaggc	19
55	<210> 172 <211> 21 <212> RNA <213> Homo sapiens	
	<400> 172 uucacagugg cuaaguuccg c	21
	<210> 173 <211> 20 <212> RNA <213> Homo sapiens	

	<400> 173 agaccauggg uucucauugu	20
5	<210> 174 <211> 23 <212> RNA <213> Homo sapiens	
10	<400> 174 ugugcuugcu cgucccgccc gca	23
15	<210> 175 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 175 ucguaccgug aguaauaauug cg	22
25	<210> 176 <211> 21 <212> RNA <213> Homo sapiens	
30	<400> 176 uucaaguaau ucaggauagg u	21
35	<210> 177 <211> 21 <212> RNA <213> Homo sapiens	
40	<400> 177 ggcuagcaac agcgcuuacc u	21
45	<210> 178 <211> 22 <212> RNA <213> Homo sapiens	
50	<400> 178 uacgucaucg uugucaucgu ca	22
55	<210> 179 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 179 cacacacugc aaauacuuuu gc	22
	<210> 180 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 180 acagcaggca cagacaggca gu	22
5	<210> 181 <211> 23 <212> RNA <213> Homo sapiens	
10	<400> 181 guccaguuuu cccaggauc ccu	23
15	<210> 182 <211> 23 <212> RNA <213> Homo sapiens	
20	<400> 182 uuaaugcuua ucgugauagg ggu	23
25	<210> 183 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 183 cucaucugca aagaaguaag ug	22
35	<210> 184 <211> 23 <212> RNA <213> Homo sapiens	
40	<400> 184 aggaccugcg ggacaagauu cuu	23
45	<210> 185 <211> 23 <212> RNA <213> Homo sapiens	
50	<400> 185 agcuacauug ucugcugggu uuc	23
55	<210> 186 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 186 uagcagcacg uaaauauugg cg	22
	<210> 187 <211> 21 <212> RNA <213> Homo sapiens	

	<400> 187 agcuacau cu ggcuacuggg u	21
5	<210> 188 <211> 23 <212> RNA <213> Homo sapiens	
10	<400> 188 uaagugcuuc cauguuuuag uag	23
15	<210> 189 <211> 19 <212> RNA <213> Homo sapiens	
20	<400> 189 aggcacggug ucagcaggc	19
25	<210> 190 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 190 agagguagua gguugcauag uu	22
35	<210> 191 <211> 21 <212> RNA <213> Homo sapiens	
40	<400> 191 aagccugccc ggcuccucgg g	21
45	<210> 192 <211> 20 <212> RNA <213> Homo sapiens	
50	<400> 192 gugcauugcu guugcauugc	20
55	<210> 193 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 193 acuggacuua gggucagaag gc	22
	<210> 194 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 194 uacucaggag aguggcaauc ac	22
5	<210> 195 <211> 23 <212> RNA <213> Homo sapiens	
10	<400> 195 uguaguguuu ccuacuuuau gga	23
15	<210> 196 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 196 aaucguacag ggucauccac uu	22
25	<210> 197 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 197 uugcauaguc acaaaaguga uc	22
35	<210> 198 <211> 21 <212> RNA <213> Homo sapiens	
40	<400> 198 ugagaugaag cacuguagcu c	21
45	<210> 199 <211> 21 <212> RNA <213> Homo sapiens	
50	<400> 199 cagcagcaca cugugguuug u	21
55	<210> 200 <211> 21 <212> RNA <213> Homo sapiens	
	<400> 200 gcuaguccug acucagccag u	21
	<210> 201 <211> 21 <212> RNA <213> Homo sapiens	

	<400> 201 auugacacuu cugugaguag a	21
5	<210> 202 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 202 uuuguucguu cggcucgcgu ga	22
15	<210> 203 <211> 23 <212> RNA <213> Homo sapiens	
20	<400> 203 aaugacacga ucacucccg uga	23
25	<210> 204 <211> 21 <212> RNA <213> Homo sapiens	
30	<400> 204 ugacaacuau ggaugagcuc u	21
35	<210> 205 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 205 aacgcacuuc ccuuuagagu gu	22
45	<210> 206 <211> 23 <212> RNA <213> Homo sapiens	
50	<400> 206 acuuacagac aagagccuug cuc	23
55	<210> 207 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 207 uauugcacau uacuaaguug ca	22
	<210> 208 <211> 24 <212> RNA <213> Homo sapiens	

	<400> 208 acaaagugcu ucccuuuaga gugu	24
5	<210> 209 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 209 uauggcacug guagaauuca cu	22
15	<210> 210 <211> 21 <212> RNA <213> Homo sapiens	
20	<400> 210 aucacauugc cagggauuac c	21
25	<210> 211 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 211 gugaaauguu uaggaccacu ag	22
35	<210> 212 <211> 23 <212> RNA <213> Homo sapiens	
40	<400> 212 uaccuguag auccgaauiu gug	23
45	<210> 213 <211> 23 <212> RNA <213> Homo sapiens	
50	<400> 213 ugucugcccg caugccugcc ucu	23
55	<210> 214 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 214 caucuaccg gacagugcug ga	22
	<210> 215 <211> 23 <212> RNA <213> Homo sapiens	

	<400> 215 agguuacccg agcaacuug cau	23
5	<210> 216 <211> 25 <212> RNA <213> Homo sapiens	
10	<400> 216 ggcggaggga aguagguccg uuggu	25
15	<210> 217 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 217 ucagugcauc acagaacuuu gu	22
25	<210> 218 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 218 cggguggauc acgaugcaau uu	22
35	<210> 219 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 219 uggcaguguc uuagcugguu gu	22
45	<210> 220 <211> 22 <212> RNA <213> Homo sapiens	
50	<400> 220 guagauucuc cuucuaugag ua	22
55	<210> 221 <211> 20 <212> RNA <213> Homo sapiens	
	<400> 221 aggguguuuc ucucaucucu	20
	<210> 222 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 222	
	uaugugggau gguaaaccgc uu	22
5	<210> 223	
	<211> 23	
	<212> RNA	
	<213> Homo sapiens	
10	<400> 223	
	ucggggauca ucaugucacg aga	23
15	<210> 224	
	<211> 23	
	<212> RNA	
	<213> Homo sapiens	
20	<400> 224	
	agugccugag ggaguaagag ccc	23
25	<210> 225	
	<211> 19	
	<212> RNA	
	<213> Homo sapiens	
30	<400> 225	
	gagccaguug gacaggagc	19
35	<210> 226	
	<211> 21	
	<212> RNA	
	<213> Homo sapiens	
40	<400> 226	
	uggguuuacg uugggagaac u	21
45	<210> 227	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
50	<400> 227	
	aagcugccag uugaagaacu gu	22
55	<210> 228	
	<211> 23	
	<212> RNA	
	<213> Homo sapiens	
	<400> 228	
	ucuggcuccg ugucuucacu ccc	23
	<210> 229	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	

	<400> 229 acaaagugcu uccuuuaga gu	22
5	<210> 230 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 230 aaaccguuac cauuacugag uu	22
15	<210> 231 <211> 23 <212> RNA <213> Homo sapiens	
20	<400> 231 caaagugcug uucgugcagg uag	23
25	<210> 232 <211> 21 <212> RNA <213> Homo sapiens	
30	<400> 232 cacaagguau ugguauuacc u	21
35	<210> 233 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 233 aucaugaugg gcuccucggu gu	22
45	<210> 234 <211> 23 <212> RNA <213> Homo sapiens	
50	<400> 234 uuucaagcca gggggcguuu uuc	23
55	<210> 235 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 235 caaagcgcuc cccuuuagag gu	22
	<210> 236 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 236 uugcauauugu aggauguccc au	22
5	<210> 237 <211> 23 <212> RNA <213> Homo sapiens	
10	<400> 237 aucgcugcgg uugcgagcgc ugu	23
15	<210> 238 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 238 uagcuuauca gacugauguu ga	22
25	<210> 239 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 239 uggaauguaa agaaguaugu au	22
35	<210> 240 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 240 ugucaguuug ucaaaauaccc ca	22
45	<210> 241 <211> 23 <212> RNA <213> Homo sapiens	
50	<400> 241 uguaaaacauc cuacacucuc agc	23
55	<210> 242 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 242 ugagguagua guuugugcug uu	22
	<210> 243 <211> 21 <212> RNA <213> Homo sapiens	

	<400> 243 ucgaggagcu cacagucuag u	21
5	<210> 244 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 244 cugcccuggc ccgagggacc ga	22
15	<210> 245 <211> 23 <212> RNA <213> Homo sapiens	
20	<400> 245 aaaagugcuu acagugcagg uag	23
25	<210> 246 <211> 23 <212> RNA <213> Homo sapiens	
30	<400> 246 uaaagugcuu auagugcagg uag	23
35	<210> 247 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 247 ucagugcacu acagaacuuu gu	22
45	<210> 248 <211> 22 <212> RNA <213> Homo sapiens	
50	<400> 248 ugagguagua gguugugugg uu	22
55	<210> 249 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 249 cagugccucg gcagugcagc cc	22
	<210> 250 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 250 uuauaaauaca accugauaag ug	22
5	<210> 251 <211> 24 <212> RNA <213> Homo sapiens	
10	<400> 251 uuuggcgaug guagaacuca cacu	24
15	<210> 252 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 252 caaaccacac ugugguguua ga	22
25	<210> 253 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 253 gcugacuccu aguccagggc uc	22
35	<210> 254 <211> 21 <212> RNA <213> Homo sapiens	
40	<400> 254 cacauuacac ggucgaccuc u	21
45	<210> 255 <211> 22 <212> RNA <213> Homo sapiens	
50	<400> 255 aacuggccua caaaguccca gu	22
55	<210> 256 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 256 ugugacuggu ugaccagagg gg	22
	<210> 257 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 257 ggugggcccg ccgugccuga gg	22
5	<210> 258 <211> 22 <212> RNA <213> Homo sapiens	
10	<400> 258 aacaucacag caagucugug cu	22
15	<210> 259 <211> 21 <212> RNA <213> Homo sapiens	
20	<400> 259 agaccuggcc cagaccucag c	21
25	<210> 260 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 260 auucugcauu uuuagcaagu uc	22
35	<210> 261 <211> 22 <212> RNA <213> Homo sapiens	
40	<400> 261 caucuacug ggcagcauug ga	22
45	<210> 262 <211> 20 <212> RNA <213> Homo sapiens	
50	<400> 262 ccucugggcc cuuccuccag	20
55	<210> 263 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 263 gaauguugcu cggugaaccc cu	22
	<210> 264 <211> 18 <212> RNA <213> Homo sapiens	

	<400> 264 uucacaggga ggugucau	18
5	<210> 265 <211> 21 <212> RNA <213> Homo sapiens	
10	<400> 265 cuuuuugcgg ucugggcuug c	21
15	<210> 266 <211> 22 <212> RNA <213> Homo sapiens	
20	<400> 266 gggggucccc ggugcucgga uc	22
25	<210> 267 <211> 22 <212> RNA <213> Homo sapiens	
30	<400> 267 aacuggcccu caaagucccg cu	22
35	<210> 268 <211> 21 <212> RNA <213> Homo sapiens	
40	<400> 268 uccucuucuc ccuccuccca g	21
45	<210> 269 <211> 23 <212> RNA <213> Homo sapiens	
50	<400> 269 ucaaauugcuc agacuccugu ggu	23
55	<210> 270 <211> 22 <212> RNA <213> Homo sapiens	
	<400> 270 gagggguuggg uggaggcucu cc	22
	<210> 271 <211> 22 <212> RNA <213> Homo sapiens	

	<400> 271	
	agggcuuagc ugcugugag ca	22
5	<210> 272	
	<211> 22	
	<212> RNA	
	<213> Homo sapiens	
10	<400> 272	
	caagcucgug ucuguggguc cg	22
	<210> 273	
	<211> 22	
15	<212> RNA	
	<213> Homo sapiens	
	<400> 273	
	ccaguggggc ugcuguuauuc ug	22
20	<210> 274	
	<211> 21	
	<212> RNA	
	<213> Homo sapiens	
25	<400> 274	
	guguugaaac aaucucuacu g	21
	<210> 275	
30	<211> 25	
	<212> RNA	
	<213> Homo sapiens	
	<400> 275	
35	agggguggug uugggacagc uccgu	25
	<210> 276	
	<211> 21	
	<212> RNA	
40	<213> Homo sapiens	
	<400> 276	
	gaacggcuuc auacaggagu u	21
45	<210> 277	
	<211> 18	
	<212> RNA	
	<213> Homo sapiens	
50	<400> 277	
	ucagcuggcc cucauuuc	18
	<210> 278	
55	<211> 23	
	<212> RNA	
	<213> Homo sapiens	

<400> 278
uucuuuuggu auaaaccgcg auu 23

5 <210> 279
<211> 22
<212> RNA
<213> Homo sapiens

10 <400> 279
aggugguccg uggcgcgguuc gc 22

15 <210> 280
<211> 22
<212> RNA
<213> Homo sapiens

20 <400> 280
aaccagcacc ccaacuugg ac 22

25 <210> 281
<211> 22
<212> RNA
<213> Homo sapiens

<400> 281
ggauaucauc auauacugua ag 22

30 <210> 282
<211> 22
<212> RNA
<213> Homo sapiens

35 <400> 282
caaagugccu cccuuuagag ug 22

40 <210> 283
<211> 22
<212> RNA
<213> Homo sapiens

45 <400> 283
gcugcgcuug gauuucgucc cc 22

Claims

50 1. A method for diagnosing an acute coronary syndrome comprising the steps of:

(i) determining an expression profile of a miRNA or a set comprising at least two miRNAs representative for an acute coronary syndrome in a blood cell sample from a human, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283, and

55 (ii) comparing said expression profile to a reference, wherein the comparison of said expression profile to said reference allows for the diagnosis of an acute coronary syndrome and/or applying an algorithm or a mathematical function to said expression profile, wherein the application of said algorithm or mathematical function to said

expression profile allows for the diagnosis of an acute coronary syndrome.

2. The method of claim 1, wherein

- (i) the algorithm or mathematical function is obtained from a reference expression profile of at least one subject with one known clinical condition which is an acute coronary syndrome, or which is no acute coronary syndrome, wherein the reference expression profile is the profile of a miRNA that has a nucleotide sequence that corresponds to the nucleotide sequence of the miRNA of step (i) or is the profile of a set comprising at least two miRNAs that have nucleotide sequences that correspond to the nucleotide sequences of the miRNAs of step (i), and/or
- (ii) the algorithm or mathematical function is obtained from reference expression profiles of at least two subjects with at least two known clinical conditions which are an acute coronary syndrome and any other known clinical condition(s), wherein the reference expression profiles are the profiles of a miRNA that has a nucleotide sequence that corresponds to the nucleotide sequence of the miRNA of step (i) or are the profiles of a set comprising at least two miRNAs that have nucleotide sequences that correspond to the nucleotide sequences of the miRNAs of step (i), wherein the two known clinical conditions are preferably an acute coronary syndrome and no acute coronary syndrome.

3. The method of claims 1 or 2, wherein

- (i) the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, preferably selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 10,
- (ii) the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 162, SEQ ID NO: 234, SEQ ID NO: 184, SEQ ID NO: 62, SEQ ID NO: 252, SEQ ID NO: 243, SEQ ID NO: 52, SEQ ID NO: 68, SEQ ID NO: 16, SEQ ID NO: 70, SEQ ID NO: 32, SEQ ID NO: 95, SEQ ID NO: 253, SEQ ID NO: 157, SEQ ID NO: 259, SEQ ID NO: 150, SEQ ID NO: 31, SEQ ID NO: 15, SEQ ID NO: 22, and SEQ ID NO: 123, or
- (iii) the nucleotide sequences of said miRNAs are selected from one or more sets listed in Figure 28 and/or Figure 30.

4. The method of claims 1 to 3, wherein the blood cells of the blood cell sample are erythrocytes, leukocytes, and/or thrombocytes.

5. The method of claims 1 to 4, wherein the acute coronary syndrome is an acute myocardial infarction (AMI).

6. The method of claim 5, wherein

- (i) the diagnosis of an acute myocardial infarction (AMI) takes place before the release of Troponin from damaged myocardium, or
- (ii) the human is Troponin negative.

7. The method of claim 5, wherein the diagnosis comprises predicting, estimating, and/or determining the size of an acute myocardial infarction (AMI).

8. The method of claims 6 or 7, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 181, SEQ ID NO: 240, and SEQ ID NO: 241.

9. Use of a polynucleotide for detecting a miRNA or a set comprising at least two polynucleotides for detecting a set comprising at least two miRNAs for diagnosing an acute coronary syndrome in a blood cell sample from a human, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283.

10. The use of claim 9, wherein

- (i) the polynucleotide is complementary to the miRNA according to claim 9, or the polynucleotides comprised in the set are complementary to the miRNAs comprised in the set according to claim 9,

(ii) the polynucleotide is a fragment of the polynucleotide according to (i), or the polynucleotides comprised in the set are fragments of the polynucleotides comprised in the set according to (i), or
 (iii) the polynucleotide has at least 80% sequence identity to the polynucleotide sequence of the polynucleotide according to (i) or polynucleotide fragment according to (ii), or the polynucleotides comprised in the set have at least 80% sequence identity to the polynucleotide sequences of the polynucleotides comprised in the set according to (i) or polynucleotide fragments comprised in the set according to (ii).

11. The use of claims 9 or 10, wherein

(i) the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 153, preferably selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 10,
 (ii) the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 162, SEQ ID NO: 234, SEQ ID NO: 184, SEQ ID NO: 62, SEQ ID NO: 252, SEQ ID NO: 243, SEQ ID NO: 52, SEQ ID NO: 68, SEQ ID NO: 16, SEQ ID NO: 70, SEQ ID NO: 32, SEQ ID NO: 95, SEQ ID NO: 253, SEQ ID NO: 157, SEQ ID NO: 259, SEQ ID NO: 150, SEQ ID NO: 31, SEQ ID NO: 15, SEQ ID NO: 22, and SEQ ID NO: 123, or
 (iii) the nucleotide sequences of said miRNAs are selected from one or more sets listed in Figure 28 and/or Figure 30.

12. The use of claims 9 to 11, wherein the blood cells of the blood cell sample are erythrocytes, leukocytes, and/or thrombocytes.

13. The use of claims 9 to 12, wherein the acute coronary syndrome is an acute myocardial infarction (AMI).

14. A kit for diagnosing an acute coronary syndrome comprising

(i) means for determining an expression profile of a miRNA or a set comprising at least two miRNAs representative for an acute coronary syndrome in a blood cell sample from a human, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 283; and
 (ii) at least one reference and/or algorithm or mathematical function, wherein the reference and/or algorithm or mathematical function are obtained from (a) reference expression profile(s) of a miRNA or a set comprising at least two miRNAs that correspond(s) to the nucleotide sequence(s) of the miRNA(s) determinable by the means of (i) in (a) blood cell sample(s) of at least two subjects with two known clinical conditions which are an acute coronary syndrome and no acute coronary syndrome, or of at least one subject with one known clinical condition which is an acute coronary syndrome or no acute coronary syndrome.

15. Use of a miRNA or a set comprising at least two miRNAs of a blood cell sample from a human as biomarker(s) for the diagnosis of an acute coronary syndrome, wherein the nucleotide sequence of said miRNA or the nucleotide sequences of said miRNAs is (are) selected from the group consisting of SEQ ID NO: 1 to 283.

Figure 1

A

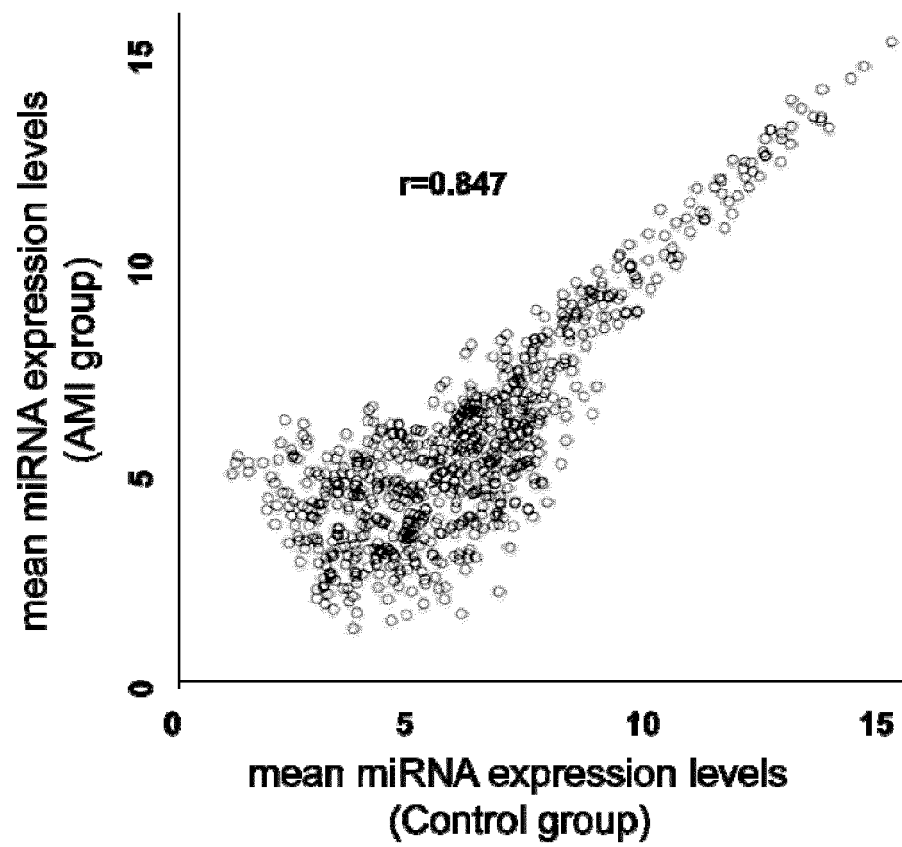


Figure 1

B

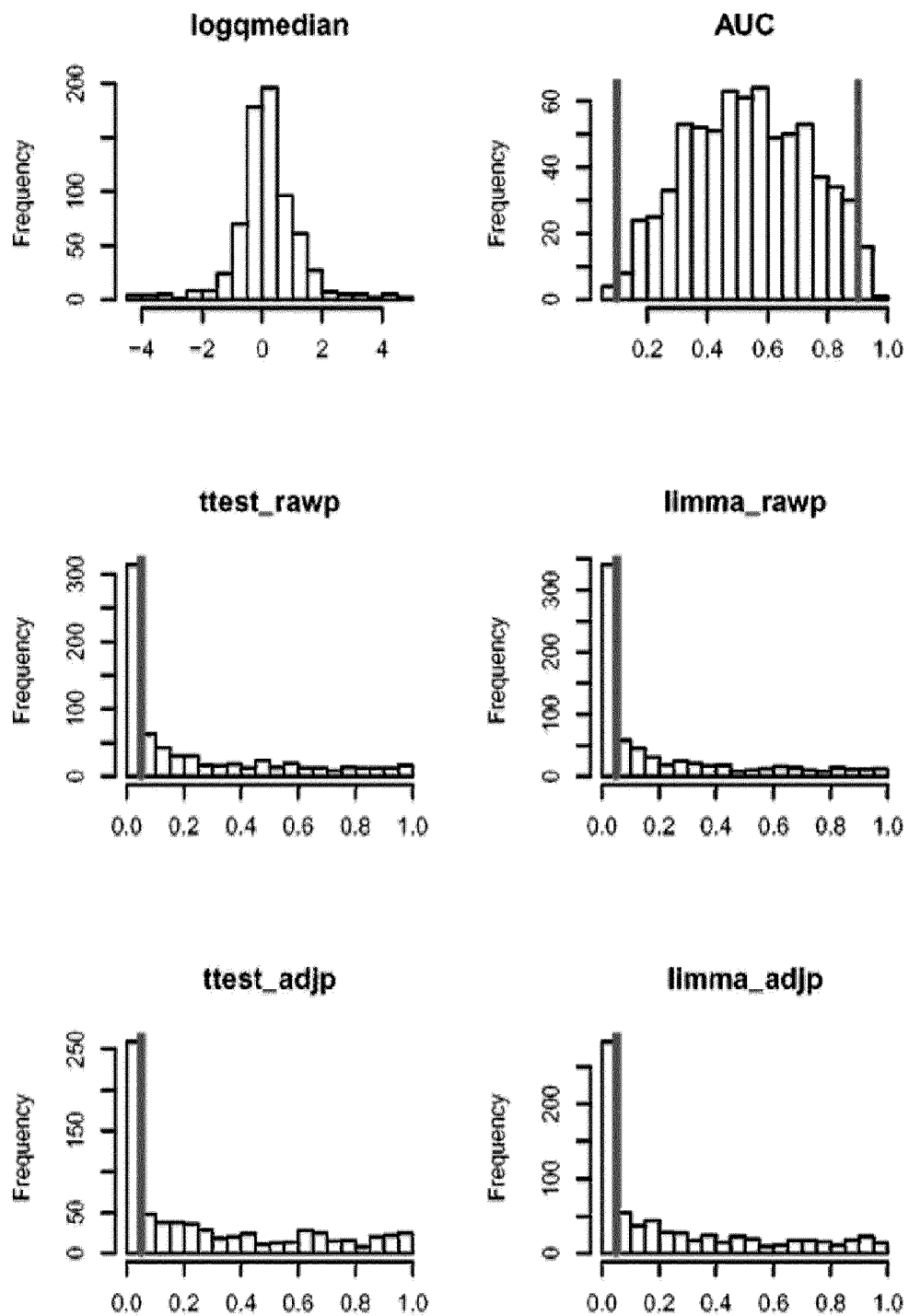


Figure 2

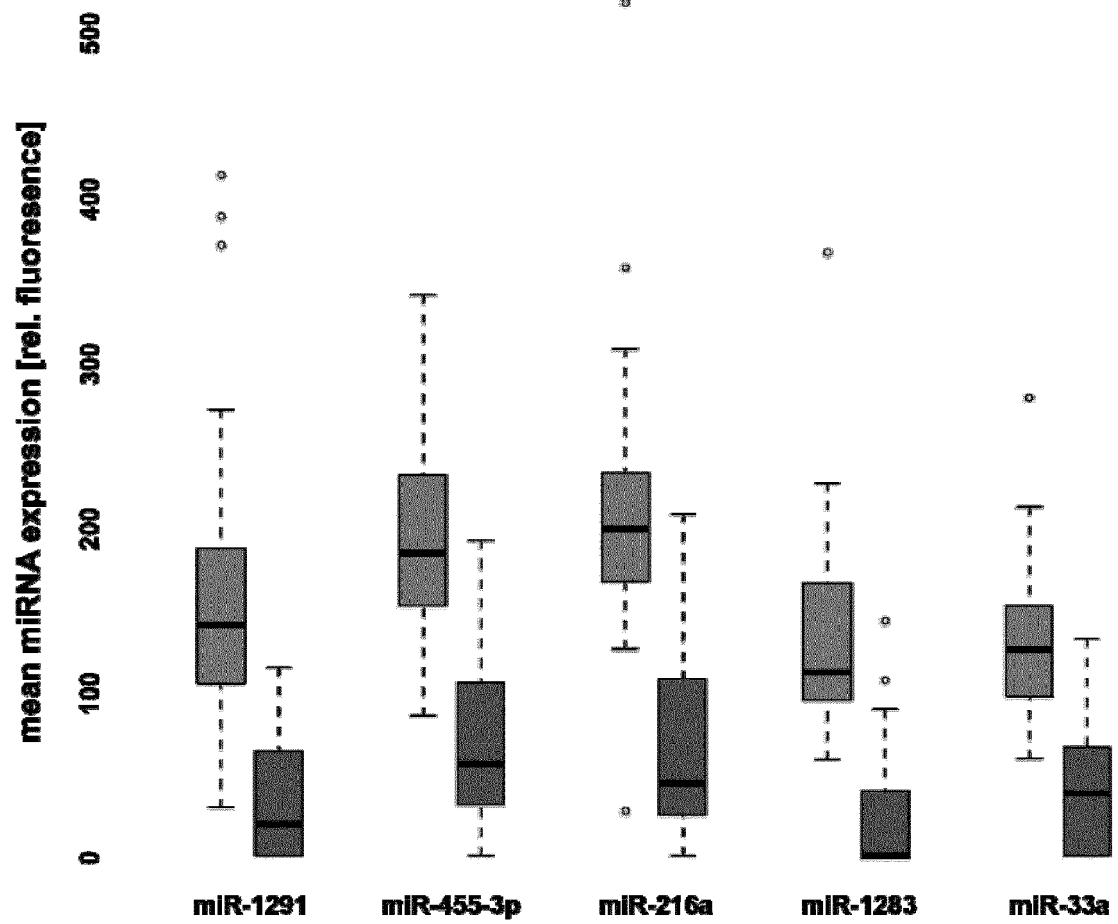


Figure 3

miR-1291

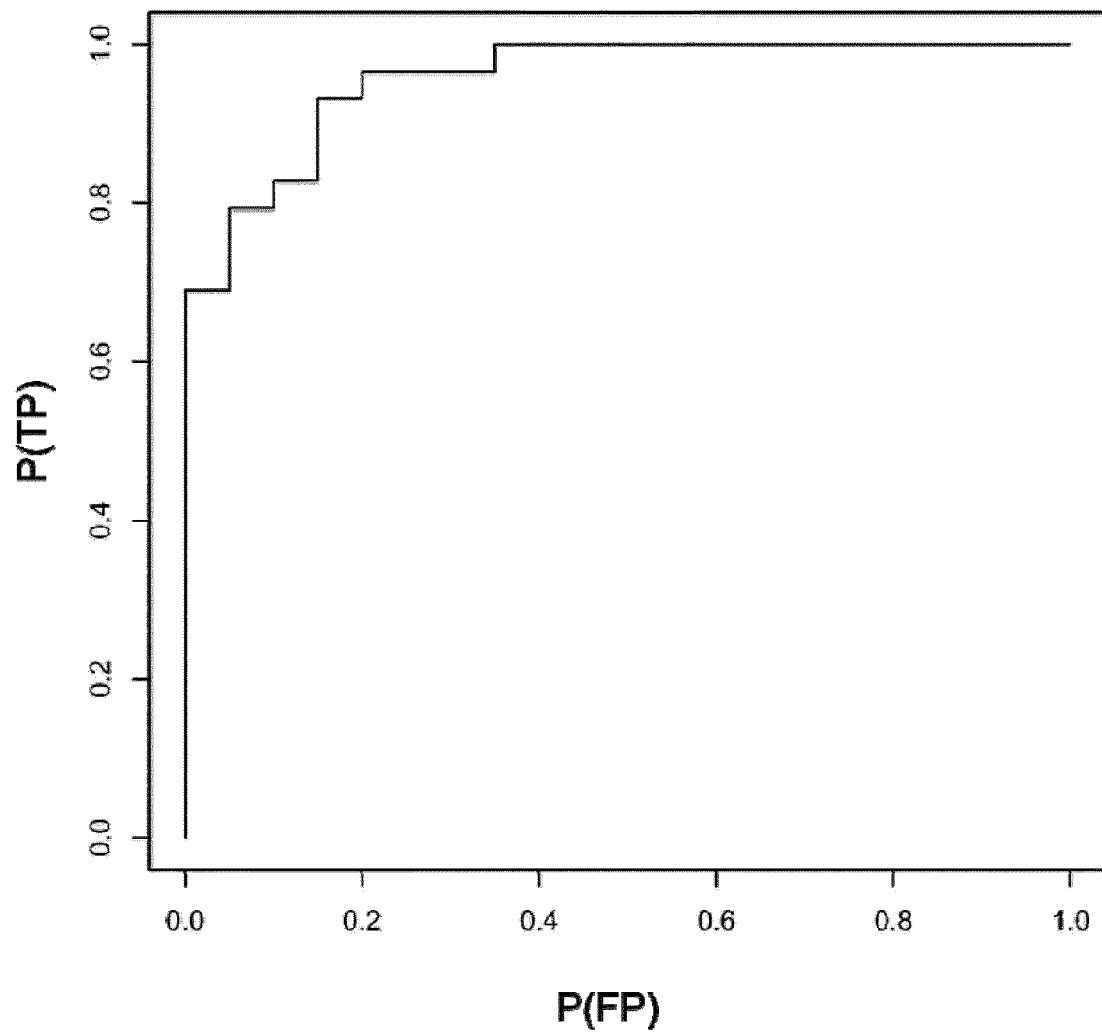


Figure 4

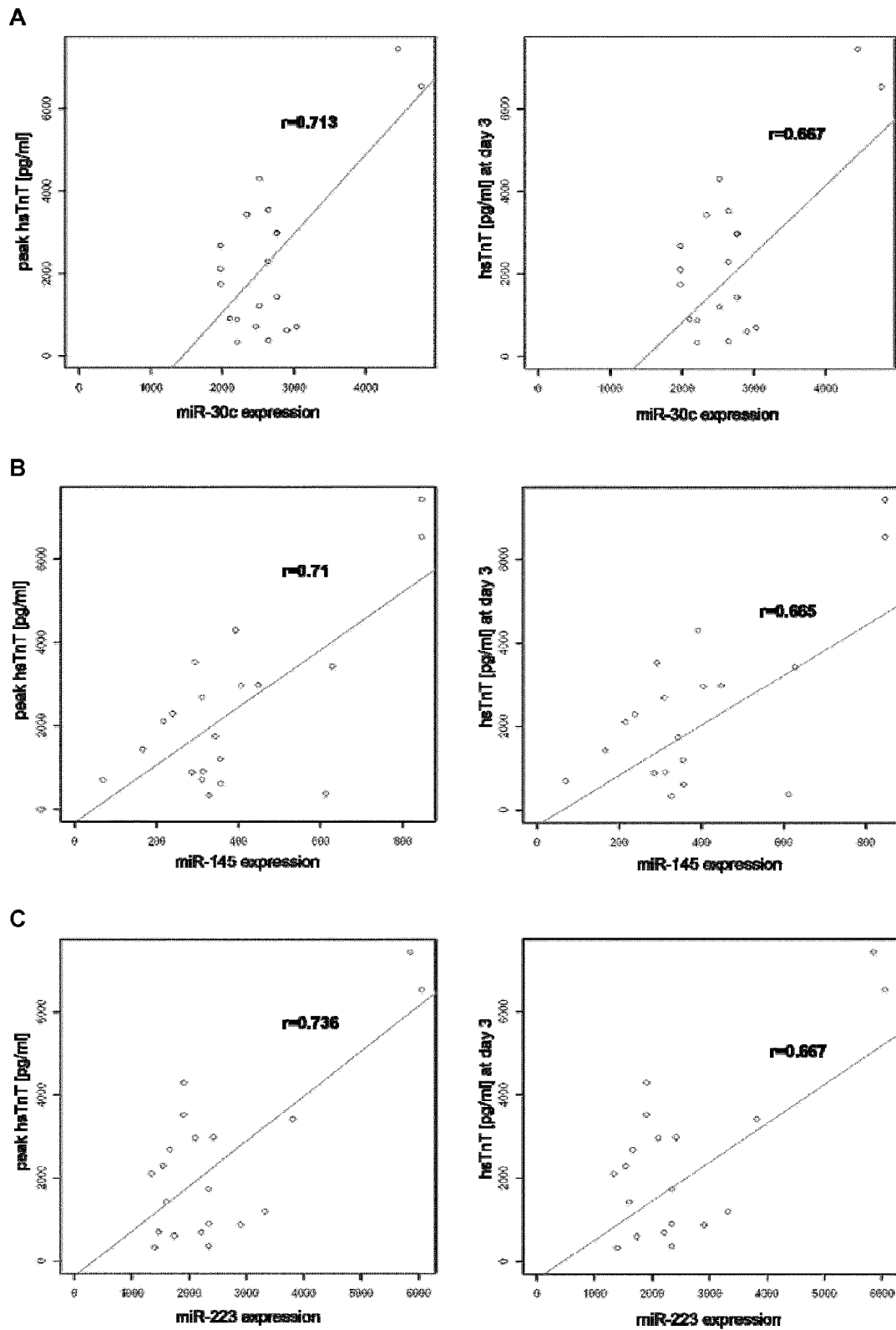


Figure 5

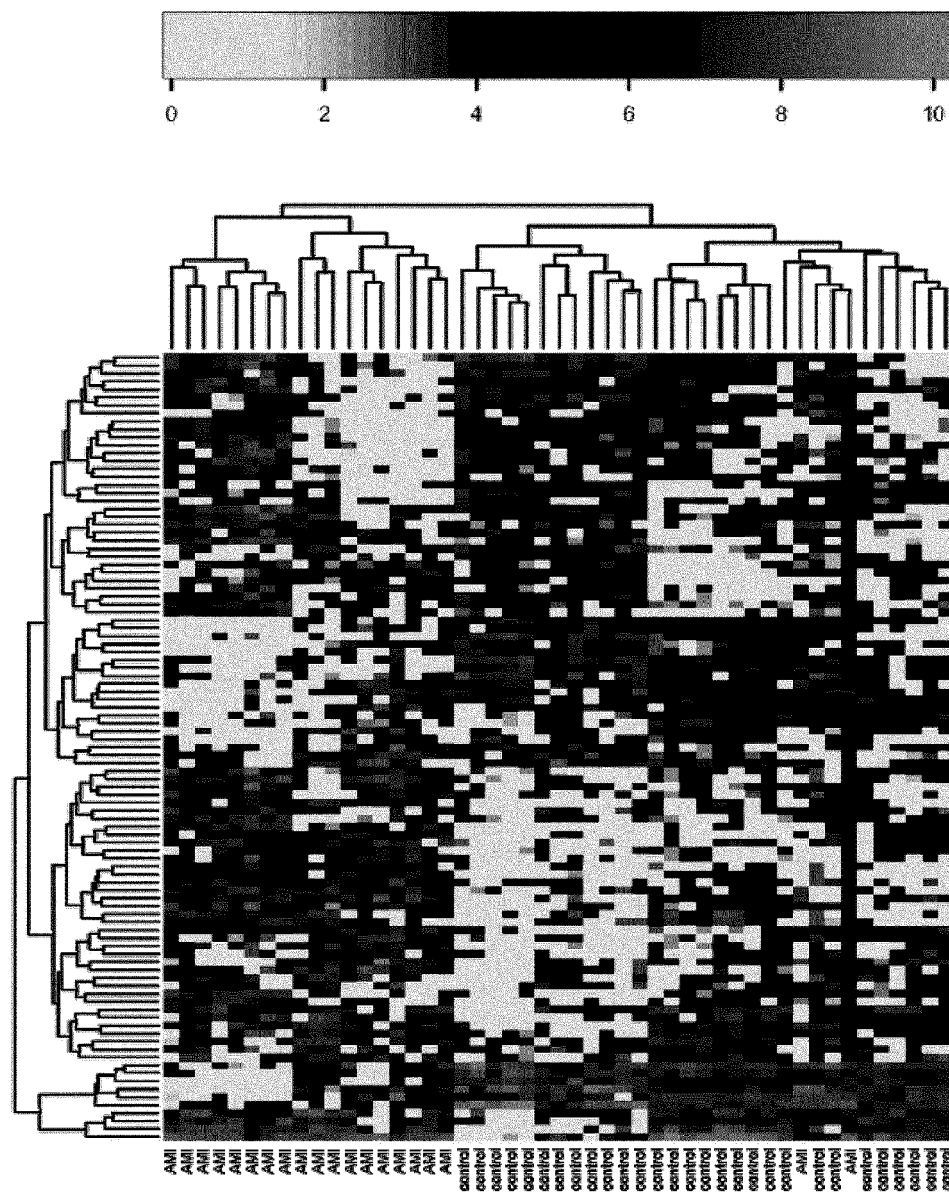
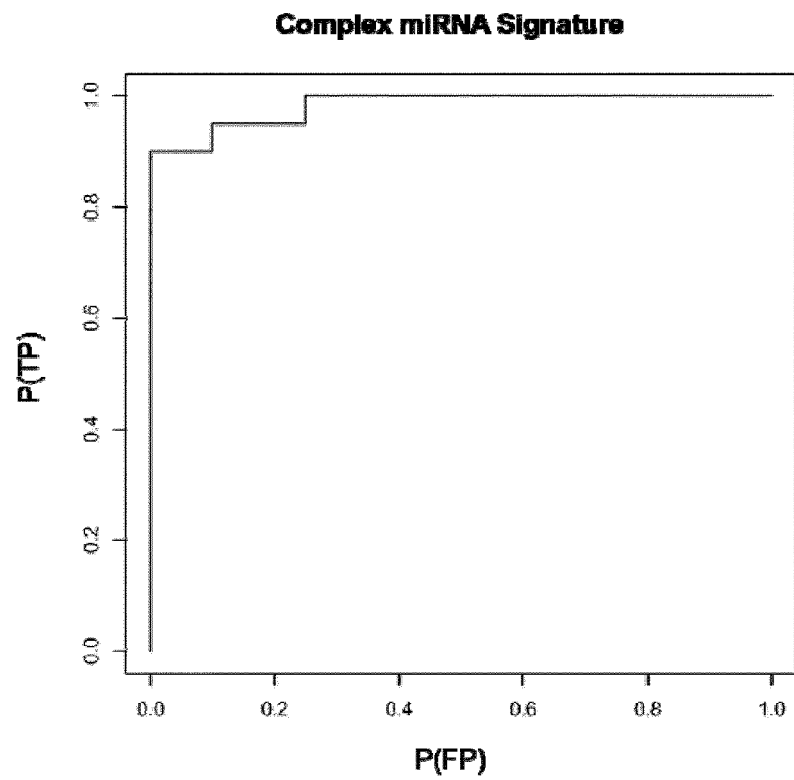


Figure 6

A



B

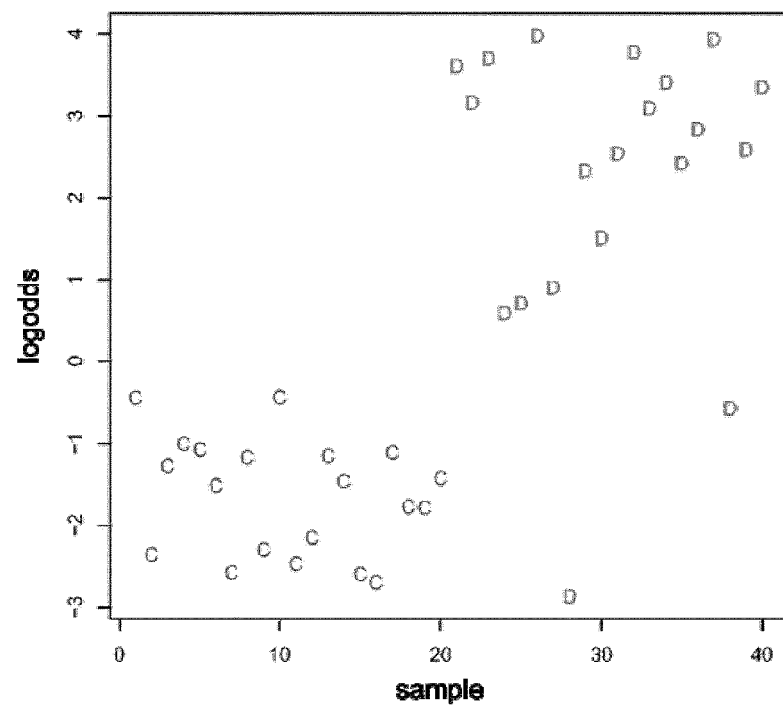


Figure 7

SEQ ID NO	miRNA	median g1	median g2	qmedian	logqmedian	ttest_rawp	ttest_adjp	limma_rawp	limma_adjp	AUC
SEQ ID NO: 1	hsa-miR-1291	9.487E+01	2.765E+01	3.431E+00	1.233E+00	8.869E-08	1.093E-05	2.243E-09	3.816E-07	0.8393
SEQ ID NO: 2	hsa-miR-1283	1.098E+02	1.000E+00	1.098E+02	4.699E+00	5.895E-08	8.480E-06	1.358E-15	1.172E-12	0.8864
SEQ ID NO: 3	hsa-miR-1201	5.959E+01	1.000E+00	5.959E+01	4.087E+00	2.877E-08	5.877E-06	1.002E-06	2.789E-05	0.8182
SEQ ID NO: 4	hsa-miR-1245	4.459E+01	3.351E+00	1.331E+01	2.588E+00	2.531E-06	1.426E-04	1.184E-05	2.171E-04	0.7936
SEQ ID NO: 5	hsa-miR-208b	6.046E+01	2.760E+01	2.191E+00	7.844E-01	5.206E-07	5.616E-05	1.096E-03	6.275E-03	0.7936
SEQ ID NO: 6	hsa-miR-1912	1.539E+02	3.334E+01	4.615E+00	1.529E+00	4.276E-05	8.021E-04	4.184E-08	2.777E-06	0.8089
SEQ ID NO: 7	hsa-miR-1278	5.447E+01	1.245E+01	4.376E+00	1.476E+00	7.988E-06	2.224E-04	1.027E-08	8.865E-07	0.8125
SEQ ID NO: 8	hsa-miR-548p	1.145E+02	5.322E+01	2.152E+00	7.683E-01	1.240E-05	3.344E-04	4.516E-05	6.720E-04	0.7793
SEQ ID NO: 9	hsa-miR-1305	9.061E+01	4.673E+01	1.939E+00	6.622E-01	3.608E-05	7.077E-04	8.662E-05	1.094E-03	0.8036
SEQ ID NO: 10	hsa-miR-1256	6.665E+01	2.636E+01	2.528E+00	9.275E-01	4.023E-05	7.716E-04	2.008E-05	3.270E-04	0.7829
SEQ ID NO: 11	hsa-miR-1226*	1.900E+02	1.100E+02	1.726E+00	5.461E-01	6.126E-05	1.017E-03	1.566E-02	4.727E-02	0.7479
SEQ ID NO: 12	hsa-miR-128	6.222E+02	4.159E+02	1.496E+00	4.030E-01	2.211E-05	5.158E-04	1.255E-02	4.012E-02	0.7754
SEQ ID NO: 13	hsa-miR-300	4.865E+01	2.011E+01	2.418E+00	8.834E-01	1.497E-05	3.798E-04	7.589E-03	2.684E-02	0.7489
SEQ ID NO: 14	hsa-miR-541	1.051E+02	2.600E+01	4.041E+00	1.397E+00	3.591E-05	7.077E-04	3.323E-05	5.208E-04	0.7871
SEQ ID NO: 15	hsa-miR-892b	2.729E+01	9.774E+01	2.792E-01	-1.278E+00	6.971E-05	1.114E-03	3.874E-05	5.865E-04	0.1518
SEQ ID NO: 16	hsa-miR-455-3p	1.706E+02	6.141E+01	2.778E+00	1.022E+00	2.724E-08	5.877E-06	1.465E-05	2.528E-04	0.8625
SEQ ID NO: 17	hsa-miR-31*	1.722E+02	3.703E+01	4.650E+00	1.537E+00	1.233E-08	5.877E-06	2.357E-10	1.017E-07	0.8575
SEQ ID NO: 18	hsa-miR-192*	1.141E+02	5.950E+01	1.918E+00	6.514E-01	2.344E-08	5.877E-06	1.613E-07	6.466E-06	0.8564
SEQ ID NO: 19	hsa-miR-767-5p	1.590E+02	5.744E+01	2.769E+00	1.018E+00	8.400E-07	7.249E-05	4.822E-06	1.015E-04	0.8154
SEQ ID NO: 20	hsa-miR-93*	1.326E+03	7.051E+02	1.881E+00	6.318E-01	1.287E-06	1.009E-04	2.863E-04	2.448E-03	0.7857
SEQ ID NO: 21	hsa-miR-155*	5.900E+01	1.648E+01	3.581E+00	1.276E+00	1.537E-06	1.105E-04	2.874E-06	6.360E-05	0.8096
SEQ ID NO: 22	hsa-miR-20b*	6.151E+01	2.671E+01	2.303E+00	8.340E-01	2.644E-06	1.426E-04	9.016E-08	4.494E-06	0.8200
SEQ ID NO: 23	hsa-miR-491-3p	7.786E+01	6.687E+00	1.164E+01	2.455E+00	2.422E-06	1.426E-04	8.068E-07	2.487E-05	0.8129
SEQ ID NO: 24	hsa-miR-330-3p	3.784E+02	1.539E+02	2.458E+00	8.995E-01	3.099E-06	1.463E-04	9.373E-08	4.494E-06	0.8479
SEQ ID NO: 25	hsa-miR-146b-5p	1.016E+02	2.233E+02	4.549E-01	-7.876E-01	3.143E-06	1.463E-04	6.001E-05	8.499E-04	0.1418
SEQ ID NO: 26	hsa-miR-556-5p	1.181E+02	4.826E+01	2.447E+00	8.950E-01	3.947E-06	1.572E-04	2.052E-06	4.786E-05	0.7882
SEQ ID NO: 27	hsa-miR-423-5p	2.877E+03	1.838E+03	1.565E+00	4.478E-01	4.278E-06	1.572E-04	6.222E-04	4.005E-03	0.7496
SEQ ID NO: 28	hsa-miR-10b*	5.144E+01	1.430E+00	3.597E+01	3.583E+00	4.371E-06	1.572E-04	2.140E-07	8.028E-06	0.8189

EP 2 865 765 A1

SEQ ID NO: 29	hsa-miR-33a	1,027E+02	4,515E+01	2,274E+00	8,215E-01	4,795E-06	1,655E-04	2,550E-04	2,317E-03	0,7939
SEQ ID NO: 30	hsa-miR-508-5p	1,139E+02	5,355E+01	2,127E+00	7,548E-01	5,179E-06	1,719E-04	9,253E-06	4,494E-06	0,8229
SEQ ID NO: 31	hsa-miR-139-5p	1,249E+02	4,741E+01	2,634E+00	9,686E-01	5,431E-06	1,736E-04	1,648E-07	6,466E-06	0,7921
SEQ ID NO: 32	hsa-miR-380*	7,294E+01	3,963E+01	1,840E+00	6,100E-01	7,435E-06	2,139E-04	1,653E-04	1,761E-03	0,7864
SEQ ID NO: 33	hsa-miR-96*	1,152E+02	5,943E+01	1,938E+00	6,616E-01	1,489E-05	3,799E-04	2,286E-03	1,061E-02	0,7529
SEQ ID NO: 34	hsa-miR-518a-3p	5,339E+01	3,830E+00	1,394E+01	2,635E+00	1,890E-05	4,660E-04	2,653E-09	3,816E-07	0,8346
SEQ ID NO: 35	hsa-miR-188-3p	1,312E+02	5,997E+01	2,187E+00	7,827E-01	2,111E-05	5,060E-04	1,532E-05	2,593E-04	0,7911
SEQ ID NO: 36	hsa-miR-20a*	1,407E+02	7,535E+01	1,868E+00	6,246E-01	2,663E-05	5,605E-04	1,083E-04	1,291E-03	0,7700
SEQ ID NO: 37	hsa-miR-520d-5p	5,975E+01	1,308E+01	4,568E+00	1,519E+00	3,123E-05	6,416E-04	4,934E-08	2,893E-06	0,7946
SEQ ID NO: 38	hsa-miR-136*	5,092E+01	1,966E+01	2,590E+00	9,515E-01	4,768E-05	8,754E-04	1,371E-03	7,168E-03	0,7543
SEQ ID NO: 39	hsa-miR-218a	1,420E+02	5,109E+01	2,780E+00	1,023E+00	5,992E-05	1,014E-03	1,572E-03	7,980E-03	0,7607
SEQ ID NO: 40	hsa-miR-532-3p	4,401E+03	2,206E+03	1,995E+00	6,906E-01	7,119E-05	1,117E-03	7,830E-05	1,024E-03	0,7943
SEQ ID NO: 41	hsa-miR-654-5p	1,820E+02	1,095E+02	1,663E+00	5,087E-01	7,936E-05	1,219E-03	5,185E-04	3,638E-03	0,7696
SEQ ID NO: 42	hsa-let-7f-1*	3,466E+01	2,969E+00	1,168E+01	2,458E+00	8,257E-05	1,229E-03	3,285E-03	1,411E-02	0,7171
SEQ ID NO: 43	hsa-miR-145*	6,006E+01	6,278E+00	9,567E+00	2,258E+00	8,512E-05	1,238E-03	6,494E-05	9,040E-04	0,7821
SEQ ID NO: 44	hsa-miR-342-3p	4,401E+03	2,787E+03	1,579E+00	4,571E-01	8,993E-05	1,252E-03	8,924E-03	3,081E-02	0,7414
SEQ ID NO: 45	hsa-miR-488*	7,382E+01	1,427E+01	5,175E+00	1,644E+00	8,938E-05	1,252E-03	4,165E-09	4,548E-07	0,8114
SEQ ID NO: 46	hsa-miR-509-5p	2,165E+02	9,090E+01	2,381E+00	8,677E-01	9,379E-05	1,285E-03	2,175E-04	2,131E-03	0,7946
SEQ ID NO: 47	hsa-miR-519b-5p	1,280E+02	3,658E+01	3,499E+00	1,253E+00	1,089E-04	1,424E-03	9,968E-07	2,789E-05	0,8007
SEQ ID NO: 48	hsa-miR-513b	4,708E+01	5,898E+00	7,982E+00	2,077E+00	1,127E-04	1,452E-03	1,351E-04	1,514E-03	0,7646
SEQ ID NO: 49	hsa-miR-550*	6,883E+02	5,058E+02	1,361E+00	3,082E-01	1,236E-04	1,668E-03	1,198E-01	2,292E-01	0,6589
SEQ ID NO: 50	hsa-miR-196a*	1,400E+02	9,250E+01	1,513E+00	4,141E-01	1,259E-04	1,575E-03	2,198E-04	2,131E-03	0,7000
SEQ ID NO: 51	hsa-miR-182b	1,952E+02	1,067E+02	1,830E+00	6,042E-01	1,530E-04	1,886E-03	2,575E-03	1,157E-02	0,7421
SEQ ID NO: 52	hsa-miR-802	5,975E+01	5,434E+00	1,100E+01	2,398E+00	1,820E-04	2,181E-03	1,208E-05	2,171E-04	0,7675
SEQ ID NO: 53	hsa-miR-1272	1,312E+02	9,220E+01	1,423E+00	3,526E-01	2,109E-04	2,459E-03	1,616E-02	4,876E-02	0,7204
SEQ ID NO: 54	hsa-miR-220c	1,037E+02	6,782E+01	1,528E+00	4,242E-01	2,371E-04	2,728E-03	8,721E-05	1,094E-03	0,7357
SEQ ID NO: 55	hsa-miR-30e*	3,940E+01	1,339E+02	2,941E-01	-1,224E+00	2,477E-04	2,813E-03	5,427E-04	3,738E-03	0,2036
SEQ ID NO: 56	hsa-miR-455-5p	1,322E+01	6,981E+01	1,893E-01	-1,664E+00	2,520E-04	2,824E-03	1,166E-04	1,326E-03	0,1796
SEQ ID NO: 57	hsa-miR-24-2*	1,506E+02	1,143E+02	1,318E+00	2,757E-01	2,652E-04	2,854E-03	6,491E-03	2,367E-02	0,6882
SEQ ID NO: 58	hsa-miR-181c*	6,030E+01	2,118E+01	2,847E+00	1,046E+00	2,699E-04	2,854E-03	2,742E-04	2,390E-03	0,7300
SEQ ID NO: 59	hsa-miR-1301	2,019E+02	1,144E+02	1,764E+00	5,676E-01	2,623E-04	2,854E-03	1,252E-02	4,012E-02	0,7293
SEQ ID NO: 60	hsa-miR-1302	3,119E+01	1,000E+00	3,119E+01	3,440E+00	3,477E-04	3,530E-03	2,170E-03	1,023E-02	0,7114
SEQ ID NO: 61	hsa-miR-933	1,763E+02	6,901E+01	2,555E+00	9,380E-01	3,620E-04	3,633E-03	9,324E-05	1,150E-03	0,7486
SEQ ID NO: 62	hsa-miR-1281	6,814E+01	1,986E+02	3,431E-01	-1,070E+00	3,851E-04	3,757E-03	4,333E-03	1,763E-02	0,2036

EP 2 865 765 A1

SEQ ID NO: 63	hsa-miR-1247	5,339E+01	1,025E+02	5,209E-01	-6,522E-01	3,974E-04	3,768E-03	1,564E-03	7,980E-03	0,2029
SEQ ID NO: 64	hsa-miR-28-5p	3,635E+02	4,953E+02	7,339E-01	-3,094E-01	4,147E-04	3,886E-03	2,974E-04	2,491E-03	0,1904
SEQ ID NO: 65	hsa-miR-876-3p	1,015E+01	7,211E+01	1,407E-01	-1,961E+00	4,595E-04	4,219E-03	2,690E-04	2,390E-03	0,2068
SEQ ID NO: 66	hsa-miR-1295	1,110E+02	6,590E+01	1,684E+00	5,210E-01	5,027E-04	4,408E-03	2,596E-02	7,112E-02	0,7232
SEQ ID NO: 67	hsa-miR-100*	6,193E+01	1,694E+01	3,658E+00	1,296E+00	5,108E-04	4,408E-03	5,482E-05	8,018E-04	0,7814
SEQ ID NO: 68	hsa-miR-23b*	2,851E+01	7,707E+01	3,699E-01	-9,944E-01	4,981E-04	4,408E-03	2,929E-03	1,283E-02	0,2071
SEQ ID NO: 69	hsa-miR-24-1*	8,704E+01	4,370E+01	1,992E+00	6,891E-01	5,365E-04	4,584E-03	2,535E-04	2,317E-03	0,7575
SEQ ID NO: 70	hsa-miR-1250	3,683E+01	1,051E+02	3,504E-01	-1,049E+00	5,579E-04	4,675E-03	3,784E-04	2,890E-03	0,2300
SEQ ID NO: 71	hsa-miR-30e	2,331E+02	4,375E+02	5,327E-01	-6,297E-01	5,765E-04	4,784E-03	7,057E-04	4,445E-03	0,2314
SEQ ID NO: 72	hsa-miR-218b	1,184E+02	8,169E+01	1,449E+00	3,707E-01	6,201E-04	5,049E-03	1,976E-02	5,724E-02	0,6946
SEQ ID NO: 73	hsa-miR-1488	1,000E+00	3,400E+01	2,941E-02	-3,528E+00	6,502E-04	5,244E-03	7,281E-06	1,496E-04	0,2114
SEQ ID NO: 74	hsa-miR-548o	9,997E+01	4,626E+01	2,161E+00	7,705E-01	6,598E-04	5,273E-03	7,461E-03	2,656E-02	0,7446
SEQ ID NO: 75	hsa-miR-1296	4,723E+01	9,664E+01	4,887E-01	-7,161E-01	7,076E-04	5,602E-03	7,086E-03	2,548E-02	0,2118
SEQ ID NO: 76	hsa-miR-942	1,575E+01	8,562E+01	1,840E-01	-1,693E+00	7,483E-04	5,871E-03	3,362E-04	2,737E-03	0,2168
SEQ ID NO: 77	hsa-miR-34a*	9,061E+01	5,350E+01	1,694E+00	5,268E-01	7,632E-04	5,933E-03	3,608E-02	9,135E-02	0,7086
SEQ ID NO: 78	hsa-miR-518e*	1,407E+02	7,505E+01	1,875E+00	6,285E-01	8,498E-04	6,548E-03	1,347E-02	4,211E-02	0,7014
SEQ ID NO: 79	hsa-miR-924	1,816E+01	1,329E+02	1,368E-01	-1,991E+00	9,163E-04	6,879E-03	1,035E-03	6,120E-03	0,2171
SEQ ID NO: 80	hsa-miR-522*	1,325E+02	6,244E+01	2,122E+00	7,526E-01	9,865E-04	7,154E-03	3,401E-04	2,743E-03	0,7386
SEQ ID NO: 81	hsa-miR-1290	1,000E+00	2,760E+01	3,624E-02	-3,318E+00	1,138E-03	7,918E-03	6,499E-10	1,870E-07	0,1211
SEQ ID NO: 82	hsa-miR-1274b	7,558E+02	1,376E+03	5,494E-01	-5,989E-01	1,157E-03	7,989E-03	4,149E-04	3,034E-03	0,2207
SEQ ID NO: 83	hsa-miR-516a-5p	1,900E+02	7,791E+01	2,439E+00	8,914E-01	1,191E-03	8,156E-03	7,748E-07	2,476E-05	0,7857
SEQ ID NO: 84	hsa-miR-1303	3,010E+01	9,537E+01	3,156E-01	-1,153E+00	1,252E-03	8,510E-03	5,072E-03	1,981E-02	0,2543
SEQ ID NO: 85	hsa-miR-140-5p	2,904E+01	8,628E+01	3,366E-01	-1,089E+00	1,575E-03	1,038E-02	5,718E-03	2,136E-02	0,2464
SEQ ID NO: 86	hsa-miR-218-1*	6,686E+01	3,778E+01	1,770E+00	5,708E-01	1,623E-03	1,061E-02	5,457E-04	3,738E-03	0,7175
SEQ ID NO: 87	hsa-miR-1271	1,509E+02	1,227E+02	1,230E+00	2,070E-01	1,687E-03	1,095E-02	2,935E-01	4,357E-01	0,5982
SEQ ID NO: 88	hsa-miR-890	3,674E+01	9,398E+00	3,910E+00	1,363E+00	1,949E-03	1,246E-02	1,898E-02	5,553E-02	0,6843
SEQ ID NO: 89	hsa-miR-190b	1,000E+00	7,505E+01	1,332E-02	-4,318E+00	1,998E-03	1,268E-02	9,746E-05	1,185E-03	0,2318
SEQ ID NO: 90	hsa-miR-938	8,635E+01	2,169E+01	3,980E+00	1,381E+00	2,220E-03	1,378E-02	5,029E-08	2,893E-06	0,7314
SEQ ID NO: 91	hsa-miR-106a*	1,318E+02	7,972E+01	1,653E+00	5,026E-01	2,248E-03	1,381E-02	2,818E-03	1,241E-02	0,7100
SEQ ID NO: 92	hsa-miR-30c-1*	3,915E+01	1,428E+01	2,741E+00	1,008E+00	2,437E-03	1,475E-02	7,705E-02	1,650E-01	0,6743
SEQ ID NO: 93	hsa-miR-891a	1,082E+02	6,913E+01	1,564E+00	4,475E-01	2,445E-03	1,475E-02	1,308E-03	6,923E-03	0,7071
SEQ ID NO: 94	hsa-miR-1266	1,129E+02	5,884E+01	1,918E+00	6,512E-01	2,511E-03	1,505E-02	5,284E-03	2,025E-02	0,7218
SEQ ID NO: 95	hsa-miR-135b*	5,332E+01	9,026E+01	5,907E-01	-5,264E-01	2,566E-03	1,527E-02	6,588E-03	2,389E-02	0,2229
SEQ ID NO: 96	hsa-miR-223*	2,888E+01	5,244E+01	5,507E-01	-5,966E-01	2,657E-03	1,568E-02	5,932E-03	2,197E-02	0,2539

EP 2 865 765 A1

SEQ ID NO: 97	hsa-miR-127-5p	1,264E+02	5,607E+01	2,254E+00	8,128E-01	2,670E-03	1,568E-02	5,359E-03	2,037E-02	0,7039
SEQ ID NO: 98	hsa-miR-1258	1,000E+00	5,874E+01	1,702E-02	-4,073E+00	2,919E-03	1,679E-02	7,759E-06	1,557E-04	0,2186
SEQ ID NO: 99	hsa-let-7f*	2,293E+02	1,209E+02	1,896E+00	6,398E-01	2,913E-03	1,679E-02	5,194E-03	2,010E-02	0,7471
SEQ ID NO: 100	hsa-miR-124	1,045E+02	5,123E+01	2,039E+00	7,127E-01	3,133E-03	1,790E-02	3,032E-04	2,516E-03	0,7050
SEQ ID NO: 101	hsa-miR-922	1,268E+02	3,463E+01	3,657E+00	1,297E+00	3,157E-03	1,792E-02	1,267E-03	6,868E-03	0,7346
SEQ ID NO: 102	hsa-miR-454	1,154E+02	2,368E+02	4,871E-01	-7,193E-01	3,205E-03	1,808E-02	8,976E-03	3,086E-02	0,2632
SEQ ID NO: 103	hsa-miR-934	8,572E+01	4,988E+01	1,715E+00	5,395E-01	3,251E-03	1,822E-02	1,858E-06	4,582E-05	0,7186
SEQ ID NO: 104	hsa-miR-339-5p	6,883E+02	3,950E+02	1,742E+00	5,552E-01	3,382E-03	1,883E-02	4,495E-02	1,072E-01	0,6807
SEQ ID NO: 105	hsa-miR-450b-5p	6,084E+01	2,438E+01	2,495E+00	9,144E-01	3,496E-03	1,922E-02	4,208E-07	1,453E-05	0,7418
SEQ ID NO: 106	hsa-miR-618*	5,447E+01	7,590E+00	7,177E+00	1,971E+00	3,665E-03	1,997E-02	1,106E-05	2,121E-04	0,7368
SEQ ID NO: 107	hsa-miR-593*	2,965E+02	1,980E+02	1,498E+00	4,040E-01	3,695E-03	1,997E-02	3,905E-02	9,657E-02	0,7204
SEQ ID NO: 108	hsa-miR-320a	1,763E+04	9,808E+03	1,798E+00	5,867E-01	3,725E-03	1,997E-02	3,648E-04	2,811E-03	0,7361
SEQ ID NO: 109	hsa-miR-379*	5,397E+01	2,245E+01	2,403E+00	8,769E-01	3,861E-03	2,057E-02	2,097E-03	9,667E-03	0,7136
SEQ ID NO: 110	hsa-miR-1270	2,066E+01	1,000E+00	2,066E+01	3,028E+00	4,029E-03	2,120E-02	1,220E-02	3,944E-02	0,6800
SEQ ID NO: 111	hsa-miR-556-3p	1,000E+00	4,722E+01	2,118E-02	-3,855E+00	4,284E-03	2,227E-02	5,959E-04	3,901E-03	0,2664
SEQ ID NO: 112	hsa-miR-17*	5,591E+02	4,617E+02	1,211E+00	1,914E-01	4,461E-03	2,298E-02	6,464E-01	7,695E-01	0,5968
SEQ ID NO: 113	hsa-miR-34b*	4,482E+01	7,649E+01	5,890E-01	-5,345E-01	4,528E-03	2,298E-02	4,663E-03	1,849E-02	0,2432
SEQ ID NO: 114	hsa-miR-1915*	2,765E+01	8,861E+00	3,121E+00	1,138E+00	4,486E-03	2,298E-02	3,660E-02	9,594E-02	0,6693
SEQ ID NO: 115	hsa-miR-509-3-5p	2,136E+02	1,312E+02	1,629E+00	4,875E-01	4,630E-03	2,336E-02	1,203E-03	6,652E-03	0,7107
SEQ ID NO: 116	hsa-miR-339-3p	2,728E+02	2,099E+02	1,299E+00	2,619E-01	4,689E-03	2,339E-02	1,363E-01	2,488E-01	0,6600
SEQ ID NO: 117	hsa-miR-320d	8,946E+02	5,561E+02	1,609E+00	4,755E-01	4,682E-03	2,339E-02	9,864E-02	1,984E-01	0,6436
SEQ ID NO: 118	hsa-miR-340*	1,586E+01	7,695E+01	2,061E-01	-1,580E+00	4,779E-03	2,370E-02	9,233E-03	3,137E-02	0,2775
SEQ ID NO: 119	hsa-miR-424*	1,110E+02	2,199E+02	5,045E-01	-6,843E-01	4,991E-03	2,437E-02	4,061E-03	1,693E-02	0,2539
SEQ ID NO: 120	hsa-miR-1204	1,935E+01	8,266E+01	2,341E-01	-1,452E+00	5,397E-03	2,610E-02	4,498E-03	1,806E-02	0,2575
SEQ ID NO: 121	hsa-miR-516a-3p	6,768E+00	4,944E+01	1,369E-01	-1,989E+00	5,415E-03	2,610E-02	3,459E-04	2,764E-03	0,2414
SEQ ID NO: 122	hsa-miR-500*	2,513E+02	1,906E+02	1,319E+00	2,765E-01	5,563E-03	2,665E-02	1,910E-01	3,119E-01	0,6911
SEQ ID NO: 123	hsa-miR-146b-3p	5,447E+01	3,756E+01	1,450E+00	3,718E-01	5,588E-03	2,665E-02	1,591E-02	4,818E-02	0,6625
SEQ ID NO: 124	hsa-miR-199a-3p	9,671E+01	1,769E+02	5,467E-01	-6,038E-01	5,694E-03	2,700E-02	8,602E-02	1,782E-01	0,2686
SEQ ID NO: 125	hsa-miR-1285	2,644E+02	1,831E+02	1,444E+00	3,675E-01	5,881E-03	2,773E-02	2,282E-03	1,061E-02	0,7232
SEQ ID NO: 126	hsa-miR-371-5p	4,348E+01	6,687E+00	6,503E+00	1,872E+00	5,945E-03	2,785E-02	1,646E-03	8,213E-03	0,6993
SEQ ID NO: 127	hsa-miR-574-3p	2,110E+03	1,653E+03	1,276E+00	2,439E-01	5,970E-03	2,785E-02	1,367E-01	2,488E-01	0,6257
SEQ ID NO: 128	hsa-miR-1262	1,000E+00	4,795E+01	2,085E-02	-3,870E+00	6,174E-03	2,865E-02	5,006E-04	3,541E-03	0,2518
SEQ ID NO: 129	hsa-miR-1537	2,729E+01	1,034E+01	2,638E+00	9,700E-01	6,499E-03	2,983E-02	8,589E-03	2,977E-02	0,7011
SEQ ID NO: 130	hsa-miR-298	1,192E+02	6,181E+01	1,929E+00	6,568E-01	6,916E-03	3,125E-02	7,522E-07	2,476E-05	0,7389

EP 2 865 765 A1

SEQ ID NO: 131	hsa-miR-582-3p	6,018E+01	5,041E+01	1,194E+00	1,772E-01	6,875E-03	3,125E-02	1,500E-01	2,663E-01	0,6539
SEQ ID NO: 132	hsa-miR-29b-2*	3,526E+01	7,305E+01	4,827E-01	-7,283E-01	7,133E-03	3,176E-02	2,284E-03	1,061E-02	0,2779
SEQ ID NO: 133	hsa-miR-548a-3p	7,070E+01	6,053E+01	1,168E+00	1,553E-01	7,386E-03	3,252E-02	2,121E-01	3,363E-01	0,6207
SEQ ID NO: 134	hsa-miR-411*	5,046E+01	9,252E+01	5,455E-01	-6,081E-01	7,350E-03	3,252E-02	1,700E-02	5,075E-02	0,2821
SEQ ID NO: 135	hsa-miR-7-1*	2,947E+02	2,102E+02	1,402E+00	3,380E-01	7,442E-03	3,260E-02	2,705E-02	7,363E-02	0,6861
SEQ ID NO: 136	hsa-miR-520a-3p	1,000E+00	3,624E+01	2,760E-02	-3,590E+00	7,513E-03	3,265E-02	2,494E-03	1,127E-02	0,2886
SEQ ID NO: 137	hsa-miR-920	2,729E+01	7,981E+01	3,415E-01	-1,075E+00	7,836E-03	3,374E-02	2,242E-04	2,150E-03	0,2293
SEQ ID NO: 138	hsa-miR-122*	4,881E+01	2,467E+01	1,979E+00	6,824E-01	7,836E-03	3,374E-02	1,061E-02	3,468E-02	0,6825
SEQ ID NO: 139	hsa-miR-615-3p	2,896E+01	8,071E+01	3,588E-01	-1,025E+00	8,548E-03	3,564E-02	3,799E-03	1,607E-02	0,2414
SEQ ID NO: 140	hsa-miR-744	6,104E+02	4,720E+02	1,293E+00	2,571E-01	8,978E-03	3,655E-02	7,259E-01	8,200E-01	0,6011
SEQ ID NO: 141	hsa-miR-875-5p	2,660E+01	7,602E+01	3,499E-01	-1,050E+00	9,254E-03	3,732E-02	1,070E-01	2,104E-01	0,2964
SEQ ID NO: 142	hsa-miR-454*	1,252E+01	3,475E+01	3,601E-01	-1,021E+00	9,747E-03	3,894E-02	3,824E-03	1,610E-02	0,2836
SEQ ID NO: 143	hsa-miR-188-5p	1,120E+02	8,382E+01	1,337E+00	2,901E-01	9,937E-03	3,952E-02	1,382E-06	3,507E-05	0,6786
SEQ ID NO: 144	hsa-miR-22*	4,639E+01	9,474E+01	4,896E-01	-7,141E-01	1,033E-02	4,061E-02	2,383E-03	1,100E-02	0,2507
SEQ ID NO: 145	hsa-miR-125a-5p	1,506E+02	2,844E+02	5,294E-01	-6,361E-01	1,029E-02	4,061E-02	3,888E-03	1,629E-02	0,2911
SEQ ID NO: 146	hsa-let-7f-2*	4,779E+00	4,113E+01	1,162E-01	-2,152E+00	1,042E-02	4,068E-02	6,501E-03	2,367E-02	0,3011
SEQ ID NO: 147	hsa-miR-483-3p	1,898E+01	4,855E+01	3,909E-01	-9,394E-01	1,052E-02	4,088E-02	5,967E-04	3,901E-03	0,2904
SEQ ID NO: 148	hsa-miR-1304	4,944E+01	7,608E+01	6,498E-01	-4,311E-01	1,154E-02	4,428E-02	1,300E-02	4,125E-02	0,2425
SEQ ID NO: 149	hsa-miR-545*	2,384E+01	1,000E+00	2,384E+01	3,171E+00	1,162E-02	4,437E-02	1,524E-03	7,831E-03	0,6800
SEQ ID NO: 150	hsa-miR-1254	1,129E+02	8,673E+01	1,301E+00	2,633E-01	1,204E-02	4,518E-02	6,375E-01	7,652E-01	0,6496
SEQ ID NO: 151	hsa-miR-92a-1*	1,406E+01	8,587E+01	1,638E-01	-1,809E+00	1,213E-02	4,532E-02	5,429E-04	3,738E-03	0,2332
SEQ ID NO: 152	hsa-miR-744*	3,994E+01	1,118E+01	3,571E+00	1,273E+00	1,231E-02	4,576E-02	1,836E-03	9,054E-03	0,7057
SEQ ID NO: 153	hsa-miR-518d-5p	1,569E+02	6,141E+01	2,555E+00	9,379E-01	1,320E-02	4,827E-02	1,770E-04	1,856E-03	0,6911
SEQ ID NO: 154	hsa-miR-26a	6,572E+03	8,933E+03	7,358E-01	-3,068E-01	3,661E-06	6,319E-06	1,293E-03	6,887E-03	0,1332
SEQ ID NO: 155	hsa-miR-484	7,714E+03	5,379E+03	1,434E+00	3,605E-01	6,588E-07	6,317E-05	2,012E-03	9,757E-03	0,7779
SEQ ID NO: 156	hsa-miR-217	1,417E+02	3,709E+01	3,821E+00	1,341E+00	1,801E-06	1,196E-04	1,597E-07	6,466E-06	0,8525
SEQ ID NO: 157	hsa-miR-566	8,653E+01	2,265E+01	3,820E+00	1,340E+00	3,222E-06	1,463E-04	4,216E-09	4,548E-07	0,8418
SEQ ID NO: 158	hsa-miR-515-5p	1,609E+02	5,121E+01	3,142E+00	1,145E+00	4,021E-06	1,572E-04	5,174E-09	4,961E-07	0,8575
SEQ ID NO: 159	hsa-miR-126*	2,133E+00	6,003E+01	3,553E-02	-3,337E+00	4,160E-06	1,572E-04	1,009E-07	4,584E-06	0,1229
SEQ ID NO: 160	hsa-miR-200a	9,031E+01	3,280E+01	2,753E+00	1,013E+00	6,329E-06	1,949E-04	1,186E-05	2,171E-04	0,8139
SEQ ID NO: 161	hsa-miR-302b*	6,685E+00	1,000E+00	6,685E+00	1,900E+00	6,549E-06	1,949E-04	1,218E-03	6,693E-03	0,7364
SEQ ID NO: 162	hsa-miR-142-5p	7,475E+02	1,183E+03	6,319E-01	-4,590E-01	2,440E-05	5,540E-04	1,285E-03	6,887E-03	0,2214
SEQ ID NO: 163	hsa-miR-519e*	6,006E+01	2,626E+00	2,287E+01	3,130E+00	2,600E-05	5,605E-04	2,360E-09	3,816E-07	0,7943
SEQ ID NO: 164	hsa-miR-512-5p	5,361E+01	1,776E+01	3,018E+00	1,105E+00	2,642E-05	5,605E-04	1,376E-06	3,507E-05	0,8064

EP 2 865 765 A1

SEQ ID NO: 165	hsa-miR-101	5,865E+02	9,854E+02	5,952E-01	-5,189E-01	4,910E-05	8,827E-04	1,634E-03	8,198E-03	0,1729
SEQ ID NO: 166	hsa-miR-489	1,562E+02	7,534E+01	2,073E+00	7,290E-01	5,385E-05	9,422E-04	5,645E-04	3,802E-03	0,7661
SEQ ID NO: 167	hsa-miR-627	1,535E+02	7,976E+01	1,924E+00	6,546E-01	5,459E-05	9,422E-04	8,899E-06	1,745E-04	0,7779
SEQ ID NO: 168	hsa-let-7g	2,694E+02	8,555E+02	3,149E-01	-1,156E+00	6,696E-05	1,090E-03	7,498E-04	4,689E-03	0,2286
SEQ ID NO: 169	hsa-miR-324-3p	8,192E+02	5,328E+02	1,537E+00	4,301E-01	8,049E-05	1,219E-03	4,119E-03	1,709E-02	0,7188
SEQ ID NO: 170	hsa-miR-568	7,147E+01	2,864E+01	2,496E+00	9,146E-01	8,605E-05	1,238E-03	8,461E-07	2,518E-05	0,7829
SEQ ID NO: 171	hsa-miR-646	2,063E+02	7,714E+01	2,675E+00	9,839E-01	1,011E-04	1,342E-03	1,784E-05	2,961E-04	0,7746
SEQ ID NO: 172	hsa-miR-27a	2,728E+02	6,416E+02	4,252E-01	-8,552E-01	1,011E-04	1,342E-03	2,955E-06	6,376E-05	0,1246
SEQ ID NO: 173	hsa-miR-591	5,361E+01	9,653E+00	5,553E+00	1,714E+00	1,744E-04	2,120E-03	3,980E-08	2,777E-06	0,7818
SEQ ID NO: 174	hsa-miR-636	1,575E+02	9,203E+01	1,711E+00	5,371E-01	1,868E-04	2,208E-03	3,912E-04	2,961E-03	0,7379
SEQ ID NO: 175	hsa-miR-128	1,620E+03	2,938E+03	5,513E-01	-5,954E-01	2,679E-04	2,854E-03	1,098E-03	6,275E-03	0,2389
SEQ ID NO: 176	hsa-miR-26b	3,229E+02	6,814E+02	4,739E-01	-7,467E-01	2,721E-04	2,854E-03	1,170E-03	6,558E-03	0,2229
SEQ ID NO: 177	hsa-miR-621	3,404E+02	1,320E+02	2,579E+00	9,473E-01	2,745E-04	2,854E-03	1,086E-03	6,275E-03	0,8200
SEQ ID NO: 178	hsa-miR-598	5,144E+01	1,150E+02	4,474E-01	-8,043E-01	3,378E-04	3,471E-03	2,453E-03	1,120E-02	0,2032
SEQ ID NO: 179	hsa-miR-603	1,152E+02	8,189E+01	1,406E+00	3,410E-01	3,829E-04	3,757E-03	7,884E-04	4,825E-03	0,7057
SEQ ID NO: 180	hsa-miR-214	3,006E+02	1,587E+02	1,895E+00	6,391E-01	3,913E-04	3,757E-03	1,603E-03	8,091E-03	0,7436
SEQ ID NO: 181	hsa-miR-145	1,264E+02	3,052E+02	4,142E-01	-8,814E-01	3,918E-04	3,757E-03	3,379E-05	5,208E-04	0,1950
SEQ ID NO: 182	hsa-miR-155	8,508E+01	1,548E+02	5,495E-01	-5,988E-01	4,190E-04	3,888E-03	2,981E-03	1,293E-02	0,2204
SEQ ID NO: 183	hsa-miR-452*	2,947E+02	1,457E+02	2,023E+00	7,046E-01	4,750E-04	4,315E-03	2,434E-03	1,118E-02	0,7414
SEQ ID NO: 184	hsa-miR-492	7,192E+01	2,129E+01	3,379E+00	1,218E+00	4,975E-04	4,408E-03	2,125E-04	2,131E-03	0,7468
SEQ ID NO: 185	hsa-miR-221	8,143E+01	1,679E+02	4,849E-01	-7,239E-01	5,076E-04	4,408E-03	2,490E-03	1,127E-02	0,2150
SEQ ID NO: 186	hsa-miR-16	1,574E+04	2,047E+04	7,689E-01	-2,628E-01	5,567E-04	4,675E-03	1,042E-02	3,421E-02	0,2550
SEQ ID NO: 187	hsa-miR-222	4,489E+02	6,383E+02	7,032E-01	-3,520E-01	6,083E-04	4,999E-03	4,196E-03	1,733E-02	0,2393
SEQ ID NO: 188	hsa-miR-302b	1,000E+00	5,271E+01	1,897E-02	-3,965E+00	8,735E-04	6,671E-03	2,318E-06	1,819E-06	0,1579
SEQ ID NO: 189	hsa-miR-564	1,565E+02	8,677E+01	1,804E+00	5,899E-01	9,318E-04	6,879E-03	1,106E-03	6,275E-03	0,7425
SEQ ID NO: 190	hsa-let-7d	2,008E+03	3,163E+03	6,346E-01	-4,547E-01	9,321E-04	6,879E-03	1,448E-02	4,464E-02	0,2407
SEQ ID NO: 191	hsa-miR-596	7,255E+01	1,190E+02	6,097E-01	-4,948E-01	9,326E-04	6,879E-03	3,537E-03	1,511E-02	0,2289
SEQ ID NO: 192	hsa-miR-33b	1,728E+02	1,314E+02	1,315E+00	2,737E-01	9,518E-04	6,961E-03	1,303E-01	2,419E-01	0,6757
SEQ ID NO: 193	hsa-miR-422a	1,385E+02	2,740E+02	5,056E-01	-6,821E-01	1,038E-03	7,408E-03	1,113E-04	1,298E-03	0,2168
SEQ ID NO: 194	hsa-miR-510	6,030E+01	2,536E+01	2,378E+00	8,661E-01	1,039E-03	7,408E-03	1,348E-03	7,092E-03	0,7336
SEQ ID NO: 195	hsa-miR-142-3p	1,784E+01	9,295E+01	1,919E-01	-1,551E+00	1,109E-03	7,844E-03	2,970E-04	2,491E-03	0,2357
SEQ ID NO: 196	hsa-miR-487b	5,424E+01	2,125E+01	2,552E+00	9,370E-01	1,127E-03	7,906E-03	3,319E-07	1,193E-05	0,7475
SEQ ID NO: 197	hsa-miR-153	1,027E+02	5,219E+01	1,967E+00	6,766E-01	1,345E-03	9,066E-03	3,593E-04	2,793E-03	0,7243
SEQ ID NO: 198	hsa-miR-143	1,701E+02	3,220E+02	5,292E-01	-6,384E-01	1,436E-03	9,605E-03	5,779E-03	2,150E-02	0,2182

EP 2 865 765 A1

SEQ ID NO: 199	hsa-miR-497	1,672E+02	9,636E+01	1,735E+00	5,512E-01	1,561E-03	1,036E-02	3,358E-04	2,737E-03	0,6850
SEQ ID NO: 200	hsa-miR-554	8,815E+01	5,057E+01	1,743E+00	5,557E-01	1,729E-03	1,114E-02	6,601E-04	4,189E-03	0,7207
SEQ ID NO: 201	hsa-miR-514	3,902E+01	7,482E+00	5,215E+00	1,652E+00	2,034E-03	1,281E-02	1,982E-03	9,664E-03	0,7089
SEQ ID NO: 202	hsa-miR-375	8,713E+00	7,070E+01	1,232E-01	-2,094E+00	2,145E-03	1,341E-02	1,092E-04	1,291E-03	0,2057
SEQ ID NO: 203	hsa-miR-425	1,198E+04	1,574E+04	7,808E-01	-2,733E-01	2,257E-03	1,381E-02	3,648E-02	9,205E-02	0,2804
SEQ ID NO: 204	hsa-miR-549	5,144E+01	2,201E+01	2,337E+00	8,491E-01	2,854E-03	1,664E-02	3,034E-03	1,309E-02	0,7186
SEQ ID NO: 205	hsa-miR-521	4,708E+01	1,192E+02	3,949E-01	-9,291E-01	3,497E-03	1,922E-02	2,330E-04	2,197E-03	0,2311
SEQ ID NO: 206	hsa-miR-600	7,396E+01	3,475E+01	2,128E+00	7,554E-01	3,716E-03	1,997E-02	4,670E-03	1,849E-02	0,6929
SEQ ID NO: 207	hsa-miR-32	1,417E+02	1,194E+02	1,187E+00	1,714E-01	3,939E-03	2,085E-02	4,529E-02	1,077E-01	0,6068
SEQ ID NO: 208	hsa-miR-520g	4,835E+01	2,453E+01	1,971E+00	8,787E-01	4,138E-03	2,164E-02	8,722E-02	1,796E-01	0,6725
SEQ ID NO: 209	hsa-miR-183	3,304E+02	6,513E+02	5,072E-01	-6,788E-01	4,527E-03	2,298E-02	2,969E-03	1,293E-02	0,2746
SEQ ID NO: 210	hsa-miR-23b	3,143E+03	3,998E+03	7,863E-01	-2,404E-01	4,858E-03	2,396E-02	1,010E-02	3,327E-02	0,2582
SEQ ID NO: 211	hsa-miR-203	8,436E+00	3,286E+01	2,567E-01	-1,360E+00	4,998E-03	2,437E-02	1,273E-03	6,866E-03	0,2657
SEQ ID NO: 212	hsa-miR-10a	4,697E+01	8,281E+01	5,673E-01	-5,669E-01	6,267E-03	2,892E-02	1,233E-01	2,338E-01	0,2757
SEQ ID NO: 213	hsa-miR-346	5,397E+01	3,646E+01	1,480E+00	3,922E-01	6,913E-03	3,125E-02	5,195E-03	2,010E-02	0,6829
SEQ ID NO: 214	hsa-miR-200a*	6,273E+01	2,935E+01	2,137E+00	7,595E-01	7,034E-03	3,162E-02	2,623E-03	1,167E-02	0,6793
SEQ ID NO: 215	hsa-miR-409-5p	7,844E+01	4,096E+01	1,915E+00	8,497E-01	7,140E-03	3,176E-02	6,008E-05	8,499E-04	0,7193
SEQ ID NO: 216	hsa-miR-658	4,881E+01	8,378E+01	5,826E-01	-5,403E-01	7,530E-03	3,265E-02	1,003E-02	3,316E-02	0,3011
SEQ ID NO: 217	hsa-miR-148b	5,277E+02	4,704E+02	1,122E+00	1,150E-01	7,618E-03	3,284E-02	2,997E-01	4,406E-01	0,6275
SEQ ID NO: 218	hsa-miR-363*	6,193E+01	4,759E+01	1,301E+00	2,635E-01	7,650E-03	3,284E-02	4,132E-04	3,034E-03	0,6764
SEQ ID NO: 219	hsa-miR-34a	2,191E+01	5,659E+01	3,871E-01	-9,490E-01	8,026E-03	3,395E-02	1,191E-03	6,631E-03	0,2643
SEQ ID NO: 220	hsa-miR-376a*	1,000E+00	4,664E+01	2,144E-02	-3,843E+00	8,155E-03	3,433E-02	2,637E-04	2,370E-03	0,2636
SEQ ID NO: 221	hsa-miR-609	1,000E+00	4,561E+01	2,192E-02	-3,820E+00	8,359E-03	3,502E-02	1,272E-05	2,239E-04	0,2132
SEQ ID NO: 222	hsa-miR-299-3p	1,450E+01	5,212E+01	2,781E-01	-1,280E+00	8,606E-03	3,571E-02	1,109E-03	6,275E-03	0,2618
SEQ ID NO: 223	hsa-miR-542-5p	8,383E+01	1,237E+02	6,777E-01	-3,891E-01	8,662E-03	3,577E-02	1,373E-02	4,279E-02	0,2964
SEQ ID NO: 224	hsa-miR-550	1,137E+02	7,423E+01	1,532E+00	4,264E-01	8,842E-03	3,621E-02	1,723E-02	5,128E-02	0,6829
SEQ ID NO: 225	hsa-miR-575	1,273E+02	7,442E+01	1,710E+00	5,365E-01	8,853E-03	3,621E-02	1,002E-02	3,316E-02	0,6675
SEQ ID NO: 226	hsa-miR-629	5,447E+01	1,574E+02	3,461E-01	-1,061E+00	9,078E-03	3,678E-02	6,263E-03	2,300E-02	0,2893
SEQ ID NO: 227	hsa-miR-22	7,714E+03	1,041E+04	7,410E-01	-2,999E-01	9,637E-03	3,868E-02	3,869E-02	9,594E-02	0,2950
SEQ ID NO: 228	hsa-miR-149	2,100E+01	6,009E+01	3,495E-01	-1,051E+00	1,035E-02	4,061E-02	3,719E-03	1,581E-02	0,2843
SEQ ID NO: 229	hsa-miR-451	1,585E+03	9,886E+02	1,603E+00	4,720E-01	1,118E-02	4,315E-02	2,808E-01	4,223E-01	0,6361
SEQ ID NO: 230	hsa-miR-520h	3,648E+01	1,000E+00	3,648E+01	3,597E+00	1,120E-02	4,315E-02	2,876E-05	4,596E-04	0,7729
SEQ ID NO: 231	hsa-miR-93	3,450E+03	4,861E+03	7,097E-01	-3,429E-01	1,169E-02	4,439E-02	1,229E-02	3,956E-02	0,2729
SEQ ID NO: 232	hsa-miR-624	5,144E+01	8,092E+01	6,357E-01	-4,330E-01	1,173E-02	4,439E-02	8,057E-02	1,704E-01	0,2850

EP 2 865 765 A1

SEQ ID NO: 233	hsa-miR-433	6,273E+01	2,760E+01	2,273E+00	8,211E-01	1,184E-02	4,460E-02	2,034E-02	5,832E-02	0,7029
SEQ ID NO: 234	hsa-miR-498	2,787E+01	5,017E+01	5,558E-01	-5,877E-01	1,235E-02	4,576E-02	9,066E-03	3,094E-02	0,2886
SEQ ID NO: 235	hsa-miR-518b	9,590E+01	5,652E+01	1,697E+00	5,288E-01	1,266E-02	4,669E-02	7,708E-03	2,715E-02	0,6989
SEQ ID NO: 236	hsa-miR-448	8,557E+01	3,480E+01	2,459E+00	8,997E-01	1,283E-02	4,710E-02	7,227E-03	2,888E-02	0,7050
SEQ ID NO: 237	hsa-miR-639	6,105E+01	4,164E+01	1,488E+00	3,826E-01	1,341E-02	4,884E-02	2,372E-04	2,201E-03	0,7054
SEQ ID NO: 238	hsa-miR-21	8,391E+02	1,252E+03	6,702E-01	-4,002E-01	2,048E-02	6,522E-02	2,172E-02	6,171E-02	0,2875
SEQ ID NO: 239	hsa-miR-1	1,322E+01	3,352E+01	3,943E-01	-9,308E-01	2,807E-02	8,385E-02	5,212E-02	1,212E-01	0,3475
SEQ ID NO: 240	hsa-miR-223	2,206E+03	1,962E+03	1,124E+00	1,169E-01	7,866E-01	8,669E-01	6,539E-01	7,714E-01	0,5246
SEQ ID NO: 241	hsa-miR-30c	2,158E+03	2,357E+03	9,153E-01	-8,853E-02	9,23E-01	9,537E-01	3,260E-01	4,720E-01	0,4454
SEQ ID NO: 242	hsa-let-7i	0,055E+04	0,085E+04	0,645E+00	-0,439E+00	0,320E+00	0,472E+00	0,031E+00	0,082E+00	
SEQ ID NO: 243	hsa-miR-151-5p	0,440E+04	0,430E+04	1,024E+00	0,024E+00	0,359E+00	0,510E+00	1,000E+00	1,000E+00	
SEQ ID NO: 244	hsa-miR-874	0,015E+04	0,015E+04	1,063E+00	0,061E+00	0,077E+00	0,174E+00	0,055E+00	0,126E+00	
SEQ ID NO: 245	hsa-miR-106a	0,592E+04	0,771E+04	0,769E+00	-0,264E+00	0,297E+00	0,450E+00	0,097E+00	0,195E+00	
SEQ ID NO: 246	hsa-miR-20a	0,362E+04	0,354E+04	1,025E+00	0,024E+00	0,624E+00	0,739E+00	0,267E+00	0,404E+00	
SEQ ID NO: 247	hsa-miR-148a	0,096E+04	0,091E+04	1,047E+00	0,046E+00	0,044E+00	0,115E+00	0,656E+00	0,771E+00	
SEQ ID NO: 248	hsa-let-7b	0,091E+04	0,102E+04	0,892E+00	-0,115E+00	0,619E+00	0,739E+00	0,110E+00	0,215E+00	
SEQ ID NO: 249	hsa-miR-33b*	0,014E+04	0,012E+04	1,115E+00	0,109E+00	0,061E+00	0,144E+00	4,503E-04	0,003E+00	
SEQ ID NO: 250	hsa-miR-374a	0,025E+04	0,045E+04	0,552E+00	-0,594E+00	0,019E+00	0,061E+00	0,022E+00	0,062E+00	
SEQ ID NO: 251	hsa-miR-182	0,420E+04	0,512E+04	0,818E+00	-0,199E+00	0,080E+00	0,178E+00	0,169E+00	0,290E+00	
SEQ ID NO: 252	hsa-miR-497*	0,010E+04	0,007E+04	1,555E+00	0,442E+00	0,057E+00	0,138E+00	0,025E+00	0,069E+00	
SEQ ID NO: 253	hsa-miR-345	0,011E+04	0,010E+04	1,072E+00	0,069E+00	0,664E+00	0,773E+00	0,417E+00	0,555E+00	
SEQ ID NO: 254	hsa-miR-323-3p	0,003E+04	0,002E+04	1,534E+00	0,428E+00	0,213E+00	0,357E+00	0,238E+00	0,368E+00	
SEQ ID NO: 255	hsa-miR-193a-3p	0,012E+04	0,008E+04	1,477E+00	0,390E+00	0,017E+00	0,058E+00	0,331E+00	0,478E+00	
SEQ ID NO: 256	hsa-miR-134	0,006E+04	0,011E+04	0,519E+00	-0,657E+00	0,060E+00	0,142E+00	0,149E+00	0,265E+00	
SEQ ID NO: 257	hsa-miR-663b	0,006E+04	0,005E+04	1,168E+00	0,155E+00	0,122E+00	0,240E+00	0,080E+00	0,169E+00	
SEQ ID NO: 258	hsa-miR-499-3p	0,006E+04	0,004E+04	1,305E+00	0,266E+00	0,029E+00	0,084E+00	0,345E+00	0,488E+00	
SEQ ID NO: 259	hsa-miR-631	0,013E+04	0,010E+04	1,261E+00	0,232E+00	0,019E+00	0,062E+00	0,101E+00	0,202E+00	
SEQ ID NO: 260	hsa-miR-544	0,004E+04	0,006E+04	0,629E+00	-0,463E+00	0,096E+00	0,206E+00	0,363E+00	0,505E+00	
SEQ ID NO: 261	hsa-miR-200b*	0,007E+04	0,009E+04	0,735E+00	-0,308E+00	0,276E+00	0,427E+00	0,393E+00	0,534E+00	
SEQ ID NO: 262	hsa-miR-326	0,009E+04	0,005E+04	1,897E+00	0,640E+00	0,018E+00	0,060E+00	0,065E+00	0,143E+00	
SEQ ID NO: 263	hsa-miR-409-3p	0,004E+04	0,007E+04	0,492E+00	-0,710E+00	0,051E+00	0,128E+00	0,044E+00	0,107E+00	
SEQ ID NO: 264	hsa-miR-513a-5p	0,005E+04	0,002E+04	2,204E+00	0,790E+00	0,018E+00	0,060E+00	0,095E+00	0,193E+00	
SEQ ID NO: 265	hsa-miR-129-5p	0,003E+04	0,005E+04	0,640E+00	-0,446E+00	0,020E+00	0,064E+00	0,062E+00	0,139E+00	
SEQ ID NO: 266	hsa-miR-615-5p	0,005E+04	0,008E+04	0,628E+00	-0,465E+00	0,016E+00	0,057E+00	0,019E+00	0,056E+00	

EP 2 865 765 A1

SEQ ID NO: 267	hsa-miR-193b	0.006E+04	0.009E+04	0.641E+00	-0.445E+00	0.024E+00	0.073E+00	0.042E+00	0.102E+00	
SEQ ID NO: 268	hsa-miR-377*	0.007E+04	0.009E+04	0.820E+00	-0.198E+00	0.585E+00	0.713E+00	0.196E+00	0.319E+00	
SEQ ID NO: 269	hsa-miR-105	0.005E+04	0.006E+04	0.857E+00	-0.154E+00	0.308E+00	0.459E+00	0.333E+00	0.478E+00	
SEQ ID NO: 270	hsa-miR-296-3p	0.005E+04	0.007E+04	0.734E+00	-0.309E+00	0.570E+00	0.702E+00	0.184E+00	0.305E+00	
SEQ ID NO: 271	hsa-miR-27a*	0.003E+04	0.006E+04	0.549E+00	-0.599E+00	0.071E+00	0.163E+00	0.159E+00	0.277E+00	
SEQ ID NO: 272	hsa-miR-99b*	0.005E+04	0.007E+04	0.749E+00	-0.289E+00	0.483E+00	0.631E+00	0.358E+00	0.501E+00	
SEQ ID NO: 273	hsa-miR-194*	0.004E+04	0.008E+04	0.552E+00	-0.595E+00	0.081E+00	0.179E+00	0.868E+00	0.916E+00	
SEQ ID NO: 274	hsa-miR-653	0.002E+04	0.002E+04	1.185E+00	0.170E+00	0.491E+00	0.637E+00	0.903E+00	0.934E+00	
SEQ ID NO: 275	hsa-miR-608	0.005E+04	0.005E+04	0.992E+00	-0.008E+00	0.509E+00	0.652E+00	0.333E+00	0.478E+00	
SEQ ID NO: 276	hsa-miR-337-5p	0.004E+04	0.003E+04	1.542E+00	0.433E+00	0.126E+00	0.246E+00	0.028E+00	0.076E+00	
SEQ ID NO: 277	hsa-miR-1207-3p	0.003E+04	0.001E+04	3.301E+00	1.194E+00	0.086E+00	0.189E+00	0.067E+00	0.146E+00	
SEQ ID NO: 278	hsa-miR-579	0.003E+04	0.003E+04	1.097E+00	0.092E+00	0.847E+00	0.904E+00	0.428E+00	0.564E+00	
SEQ ID NO: 279	hsa-miR-323-5p	0.005E+04	0.010E+04	0.459E+00	-0.780E+00	0.017E+00	0.059E+00	0.002E+00	0.010E+00	
SEQ ID NO: 280	hsa-miR-634	0.010E+04	0.003E+04	3.860E+00	1.351E+00	0.027E+00	0.078E+00	0.715E-04	9.645E-04	
SEQ ID NO: 281	hsa-miR-144*	0.065E+04	0.065E+04	0.999E+00	-0.001E+00	0.891E+00	0.930E+00	0.202E+00	0.325E+00	
SEQ ID NO: 282	hsa-miR-519d	0.006E+04	0.007E+04	0.799E+00	-0.224E+00	0.154E+00	0.282E+00	0.116E+00	0.222E+00	
SEQ ID NO: 283	hsa-miR-191*	0.005E+04	0.003E+04	1.729E+00	0.548E+00	0.808E+00	0.732E+00	0.339E+00	0.485E+00	

Figure 8

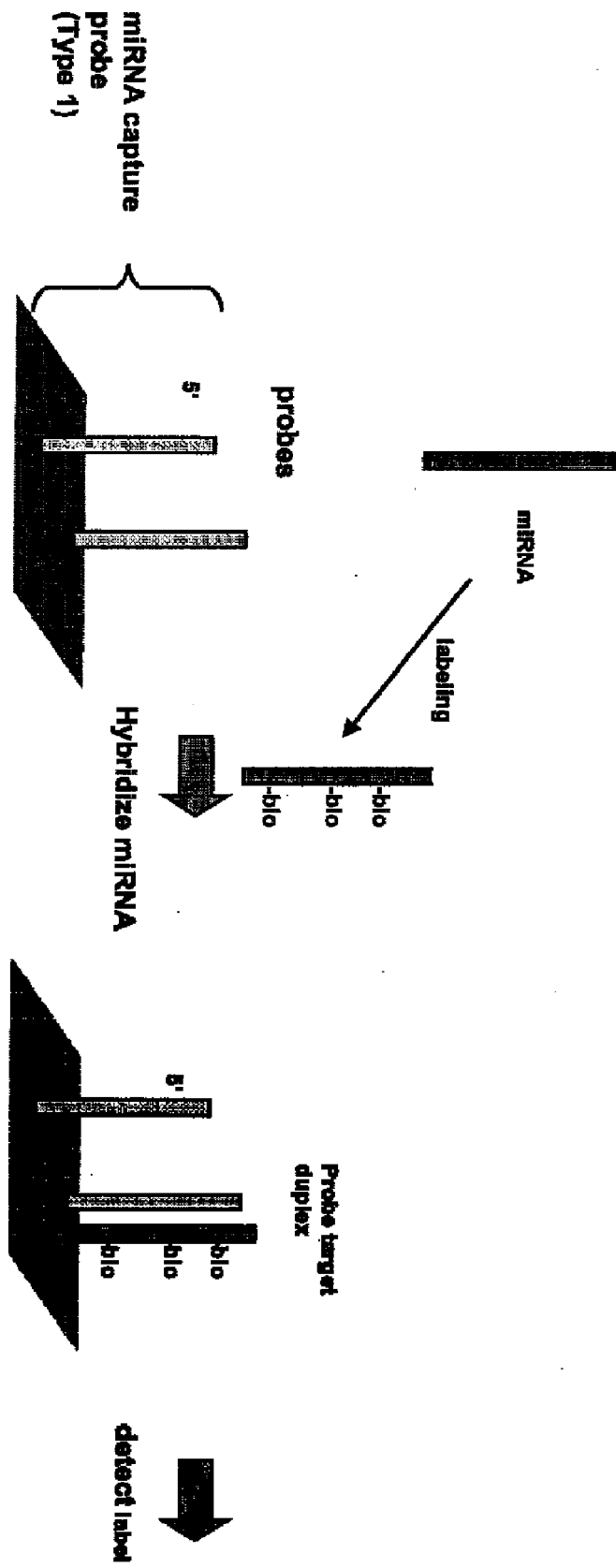
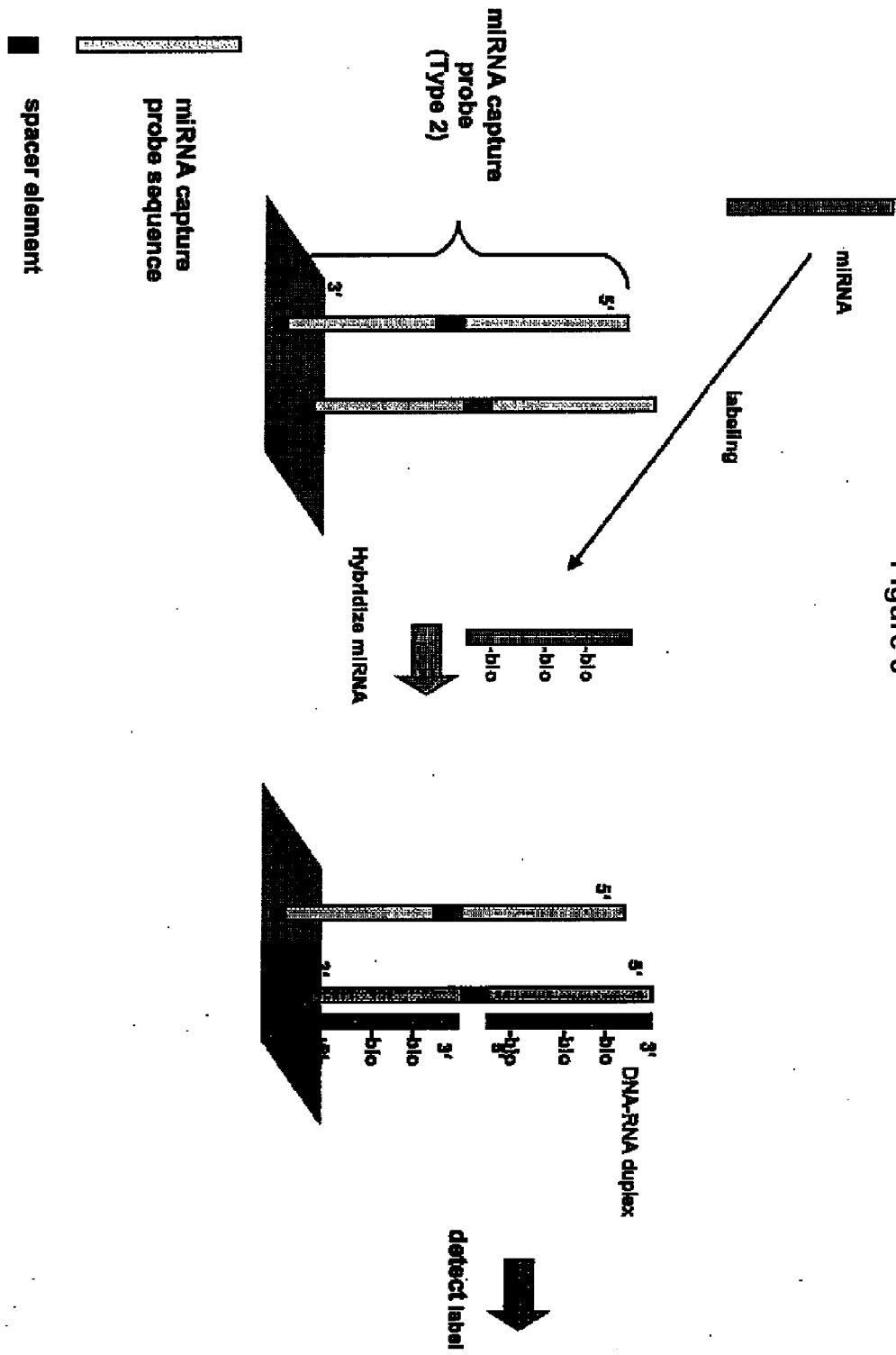


Figure 9



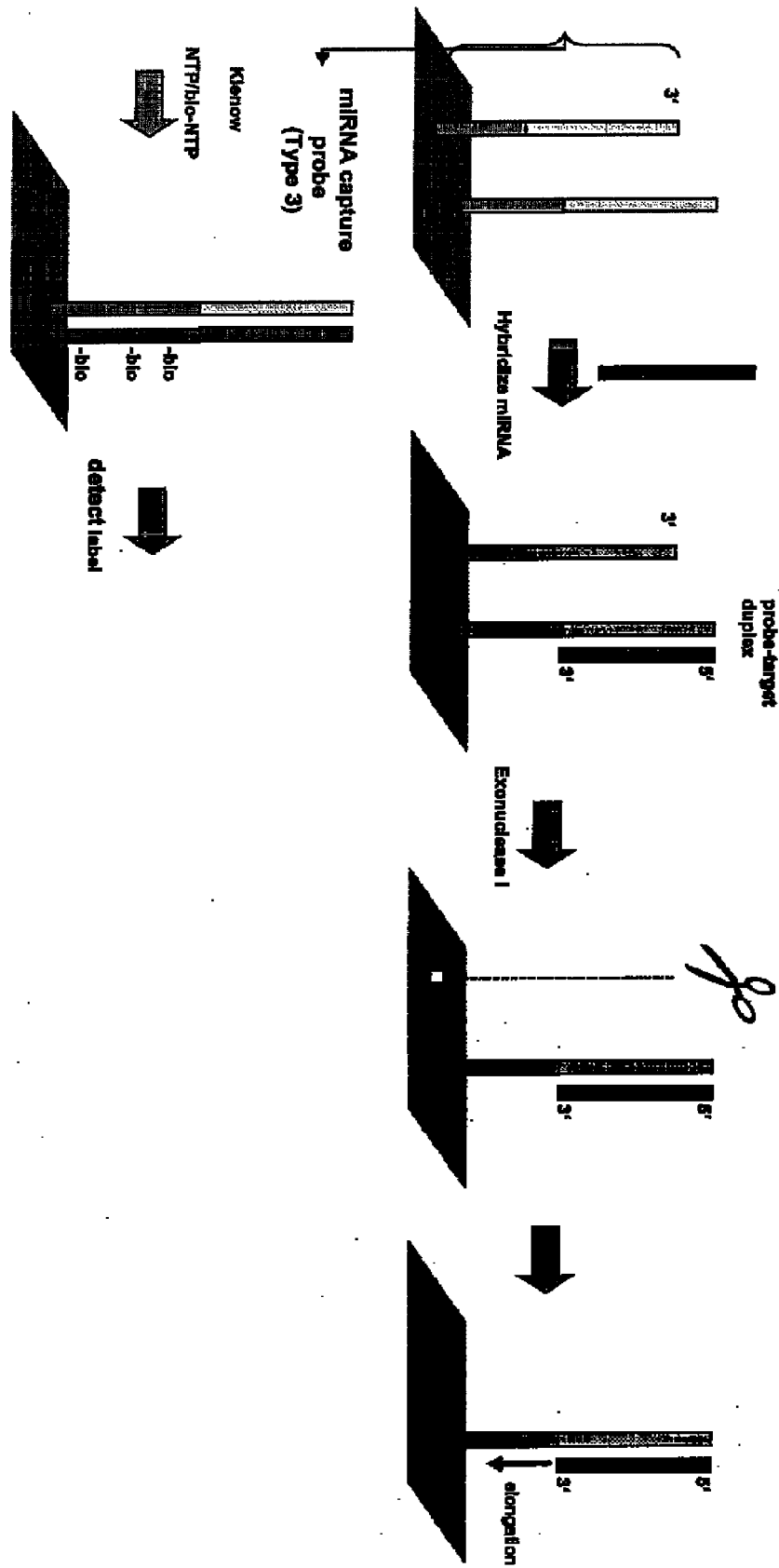


Figure 10

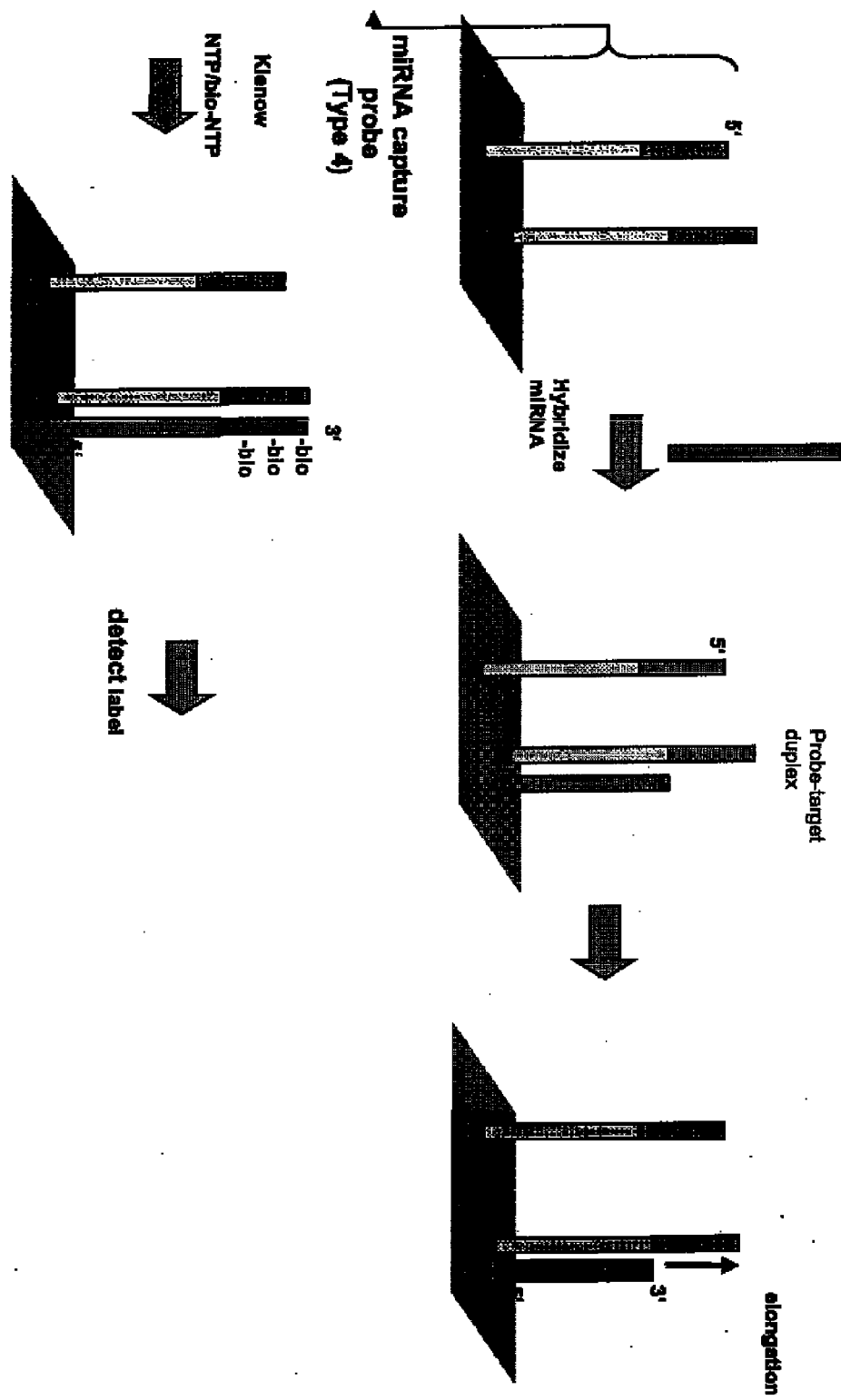


Figure 11

Figure 12

SEQ ID NO:	miRNA	Sequences 5'--3'
SEQ ID NO: 1	hsa-miR-1291	UGGCCCUGACUGAAGACCAGCAGU
SEQ ID NO: 2	hsa-miR-1283	UCUACAAAGGAAAGCGCUUUCU
SEQ ID NO: 3	hsa-miR-1201	AGCCUGAUUAAACACAUGCUCUGA
SEQ ID NO: 4	hsa-miR-1245	AAGUGAUCUAAAGGCCUACAU
SEQ ID NO: 5	hsa-miR-208b	AUAAGACGAACAAAAGGUUUGU
SEQ ID NO: 6	hsa-miR-1912	UACCCAGAGCAUGCAGUGUGAA
SEQ ID NO: 7	hsa-miR-1278	UAGUACUGUGCAUAUCAUCUUAU
SEQ ID NO: 8	hsa-miR-548p	UAGCAAAAACUGCAGUUACUUU
SEQ ID NO: 9	hsa-miR-1305	UUUUC AACUCUAAUUGGAGAGA
SEQ ID NO: 10	hsa-miR-1256	AGGCAUUGACUUCUCACUAGCU
SEQ ID NO: 11	hsa-miR-1226*	GUGAGGGCAUGCAGGCCUGGAUGGGG
SEQ ID NO: 12	hsa-miR-128	UCACAGUGAACCGGUCUCUUU
SEQ ID NO: 13	hsa-miR-300	UAUACAAGGGCAGACUCUCUCU
SEQ ID NO: 14	hsa-miR-541	UGGUGGGCACAGAAUCUGGACU
SEQ ID NO: 15	hsa-miR-892b	CACUGGCUCUUUCUGGGUAGA
SEQ ID NO: 16	hsa-miR-455-3p	GCAGUCCAUGGGCAUAUACAC
SEQ ID NO: 17	hsa-miR-31*	UGCUAUGCCAACAUUUGCCAU
SEQ ID NO: 18	hsa-miR-192*	CUGCCAAUCCAUAAGGUCACAG
SEQ ID NO: 19	hsa-miR-767-5p	UGCACCAUGGUUGUCUGAGCAUG
SEQ ID NO: 20	hsa-miR-93*	ACUGCUGAGCUAGCACUCCCCG
SEQ ID NO: 21	hsa-miR-155*	CUCCUACAUAUUAGCAUUAACA
SEQ ID NO: 22	hsa-miR-20b*	ACUGUAGUAUGGGCACUCCAG
SEQ ID NO: 23	hsa-miR-491-3p	CUUAUGCAAGAUUCCCUUCUAC
SEQ ID NO: 24	hsa-miR-330-3p	GCAAAGCACACGGCCUGCAGAGA
SEQ ID NO: 25	hsa-miR-146b-5p	UGAGAACUGAAUCCAUAAGGCU
SEQ ID NO: 26	hsa-miR-556-5p	GAUGAGCUCAUUGUAAUAUAG
SEQ ID NO: 27	hsa-miR-423-5p	UGAGGGGCAGAGAGCGAGACUUU
SEQ ID NO: 28	hsa-miR-10b*	ACAGAUUCGAUUCUAGGGGAU
SEQ ID NO: 29	hsa-miR-33a	GUGCAUUGUAGUUGCAUUGCA
SEQ ID NO: 30	hsa-miR-508-5p	UACUCCAGAGGGCGUCACUCAUG
SEQ ID NO: 31	hsa-miR-139-5p	UCUACAGUGCACGUGUCUCCAG
SEQ ID NO: 32	hsa-miR-380*	UGGUUGACCAUAGAACAUGCGC
SEQ ID NO: 33	hsa-miR-96*	AAUCAUGUGCAGUGCCAAUAUG
SEQ ID NO: 34	hsa-miR-518a-3p	GAAAGCGCUUCCCUUUGCUGGA
SEQ ID NO: 35	hsa-miR-188-3p	CUCCCACAUGCAGGGUUUGCA
SEQ ID NO: 36	hsa-miR-20a*	ACUGCAUUAUGAGCACUAAAG
SEQ ID NO: 37	hsa-miR-520d-5p	CUACAAAGGGAAGCCCUUUC
SEQ ID NO: 38	hsa-miR-136*	CAUCAUCGUCUCAAUAGAGUCU
SEQ ID NO: 39	hsa-miR-216a	UAAUCUCAGCUGGCAACUGUGA
SEQ ID NO: 40	hsa-miR-532-3p	CCUCCACACCCAAGGCUUGCA
SEQ ID NO: 41	hsa-miR-654-5p	UGGUGGGCCGCAGAACAUUGUC
SEQ ID NO: 42	hsa-let-7f-1*	CUAUACAAUCUAUUGCCUCCC
SEQ ID NO: 43	hsa-miR-145*	GGAUUCUGGAAAUACUGUUCU
SEQ ID NO: 44	hsa-miR-342-3p	UCUCACACAGAAUUCGCACCCGU
SEQ ID NO: 45	hsa-miR-488*	CCCAGAUAAUGGCACUCUCAA
SEQ ID NO: 46	hsa-miR-509-5p	UACUGCAGACAGUGGCAAUCA
SEQ ID NO: 47	hsa-miR-519b-5p	CUCUAGAGGGAAGCGCUUUCUG
SEQ ID NO: 48	hsa-miR-513b	UUCACAAGGAGGUGUCAUUUAU
SEQ ID NO: 49	hsa-miR-550*	UGUCUACUCCCUAGGCCACAU

SEQ ID NO: 50	hsa-miR-196a*	CGGCAACAAGAAACUGCCUGAG
SEQ ID NO: 51	hsa-miR-1826	AUUGAUCAUCGACACUUCGAACGCAAU
SEQ ID NO: 52	hsa-miR-802	CAGUAACAAAGAUUCAUCCUUGU
SEQ ID NO: 53	hsa-miR-1272	GAUGAUGAUGGCAGCAAAUUCUGAAA
SEQ ID NO: 54	hsa-miR-220c	ACACAGGGCUGUUGUGAAGACU
SEQ ID NO: 55	hsa-miR-30e*	CUUUCAGUCGGAUGUUUACAGC
SEQ ID NO: 56	hsa-miR-455-5p	UAUGUGCCUUUGGACUACAUCG
SEQ ID NO: 57	hsa-miR-24-2*	UGCCUACUGAGCUGAAACACAG
SEQ ID NO: 58	hsa-miR-181c*	AACCAUCGACCGUUGAGUGGAC
SEQ ID NO: 59	hsa-miR-1301	UUGCAGCUGCCUGGGAGUGACUUC
SEQ ID NO: 60	hsa-miR-1302	UUGGGACAUACUUAUGCUAAA
SEQ ID NO: 61	hsa-miR-933	UGUGCGCAGGGAGACCUCUCCC
SEQ ID NO: 62	hsa-miR-1281	UCGCCUCCUCCUCUCCC
SEQ ID NO: 63	hsa-miR-1247	ACCCGUCCCGUUCGUCCCCGGA
SEQ ID NO: 64	hsa-miR-28-5p	AAGGAGCUCACAGUCUAUUGAG
SEQ ID NO: 65	hsa-miR-876-3p	UGGUGGUUUACAAAGUAAUUCA
SEQ ID NO: 66	hsa-miR-1295	UUAGGCCGCAGAUUCUGGGUGA
SEQ ID NO: 67	hsa-miR-100*	CAAGCUUGUAUCUAUAGGU AUG
SEQ ID NO: 68	hsa-miR-23b*	UGGGUUCUGGCAUGCUGAUUU
SEQ ID NO: 69	hsa-miR-24-1*	UGCCUACUGAGCUGAUUACAGU
SEQ ID NO: 70	hsa-miR-1250	ACGGUGCUGGAUGUGGCCUUU
SEQ ID NO: 71	hsa-miR-30e	UGUAAACAUCUUGACUGGAAG
SEQ ID NO: 72	hsa-miR-216b	AAAUCUCUGCAGGCAAUGUGA
SEQ ID NO: 73	hsa-miR-1468	CUCCGUUUGCCUGUUUCGCUG
SEQ ID NO: 74	hsa-miR-548o	CCAAAACUGCAGUUACUUUUGC
SEQ ID NO: 75	hsa-miR-1296	UUAGGGCCUGGCUCCAUCUCC
SEQ ID NO: 76	hsa-miR-942	UCUUCUCUGUUUUGGCCAUGUG
SEQ ID NO: 77	hsa-miR-34a*	CAAUCAGCAAGUAUACUGCCCU
SEQ ID NO: 78	hsa-miR-518e*	CUCUAGAGGGAAGCGCUUUCUG
SEQ ID NO: 79	hsa-miR-924	AGAGUCUUGUGAUGUCUUGC
SEQ ID NO: 80	hsa-miR-522*	CUCUAGAGGGAAGCGCUUUCUG
SEQ ID NO: 81	hsa-miR-1290	UGGAUUUUUGGAUCAGGGA
SEQ ID NO: 82	hsa-miR-1274b	UCCCUGUUCGGGCGCCA
SEQ ID NO: 83	hsa-miR-516a-5p	UUCUCGAGGAAAGAAGCACUUUC
SEQ ID NO: 84	hsa-miR-1303	UUUAGAGACGGGGUCUUGCUCU
SEQ ID NO: 85	hsa-miR-140-5p	CAGUGGUUUUACCCUAUGGUAG
SEQ ID NO: 86	hsa-miR-218-1*	AUGGUUCCGUCAAGCACCAUGG
SEQ ID NO: 87	hsa-miR-1271	CUUGGCACCUAGCAAGCACUCA
SEQ ID NO: 88	hsa-miR-890	UACUUGGAAAGGCAUCAGUUG
SEQ ID NO: 89	hsa-miR-190b	UGAUUUGUUUGAUUUGGGUU
SEQ ID NO: 90	hsa-miR-938	UGCCCUUAAAGGUGAACCCAGU
SEQ ID NO: 91	hsa-miR-106a*	CUGCAAUGUAAGCACUUCUAC
SEQ ID NO: 92	hsa-miR-30c-1*	CUGGGAGAGGGUUGUUUACUCC
SEQ ID NO: 93	hsa-miR-891a	UGCAACGAACCUGAGCCACUGA
SEQ ID NO: 94	hsa-miR-1266	CCUCAGGGCUGUAGAACAGGGCU
SEQ ID NO: 95	hsa-miR-135b*	AUGUAGGGCUAAAAGCCAUGGG
SEQ ID NO: 96	hsa-miR-223*	CGUGUAAUUGACAAGCUGAGUU
SEQ ID NO: 97	hsa-miR-127-5p	CUGAAGCUCAGAGGGCUCUGAU
SEQ ID NO: 98	hsa-miR-1258	AGUUAGGAUUAAGGUCUGGAA
SEQ ID NO: 99	hsa-let-7i*	CUGCGCAAGCUACUGCCUUGCU
SEQ ID NO: 100	hsa-miR-124	UAAGGCACGCGGUGAAUGCC
SEQ ID NO: 101	hsa-miR-922	GCAGCAGAGAAUAGGACUACGUC
SEQ ID NO: 102	hsa-miR-454	UAGUGCAAUUAUGCUUAUAGGGU

EP 2 865 765 A1

SEQ ID NO: 103	hsa-miR-934	UGUCUACUACUGGAGACACUGG
SEQ ID NO: 104	hsa-miR-339-5p	UCCCUGUCCUCCAGGAGCUCACG
SEQ ID NO: 105	hsa-miR-450b-5p	UUUUGCAAUAUGUCCUGAAUA
SEQ ID NO: 106	hsa-miR-616*	ACUCAAACCCUUCAGUGACUU
SEQ ID NO: 107	hsa-miR-593*	AGGCACCAGCCAGGCAUUGCUCAGC
SEQ ID NO: 108	hsa-miR-320a	AAAAGCUGGGUUGAGAGGGCGA
SEQ ID NO: 109	hsa-miR-379*	UAUGUAACAUGGUCCACUAACU
SEQ ID NO: 110	hsa-miR-1270	CUGGAGAUUUGGAAGAGCUGUGU
SEQ ID NO: 111	hsa-miR-556-3p	AUAUUACCAUUGAGCUCAUCUUU
SEQ ID NO: 112	hsa-miR-17*	ACUGCAGUGAAGGCACUUGUAG
SEQ ID NO: 113	hsa-miR-34b*	UAGGCAGUGUAUUGCGUAUUG
SEQ ID NO: 114	hsa-miR-1915*	ACCUUGCCUUGCUGCCCCGGGCC
SEQ ID NO: 115	hsa-miR-509-3-5p	UACUGCAGACGUGGCAAUCAUG
SEQ ID NO: 116	hsa-miR-339-3p	UGAGCGCCUCGACGACAGAGCCG
SEQ ID NO: 117	hsa-miR-320d	AAAAGCUGGGUUGAGAGGA
SEQ ID NO: 118	hsa-miR-340*	UCCGUCUCAGUUACUUUAUAGC
SEQ ID NO: 119	hsa-miR-424*	CAAAACGUGAGGGCGUCUAU
SEQ ID NO: 120	hsa-miR-1204	UCGUGGCCUGGUCUCCAUAU
SEQ ID NO: 121	hsa-miR-516a-3p	UGCUUCCUUUCAGAGGGU
SEQ ID NO: 122	hsa-miR-500*	AUGCACCUGGGCAAGGAUUCUG
SEQ ID NO: 123	hsa-miR-146b-3p	UGCCCUGUGGACUCAGUUCUGG
SEQ ID NO: 124	hsa-miR-199a-3p	ACAGUAGUCUGCACAUGGUUA
SEQ ID NO: 125	hsa-miR-1285	UCUGGGCAACAAAGUGAGACCU
SEQ ID NO: 126	hsa-miR-371-5p	ACUCAAAACUGUGGGGGCACU
SEQ ID NO: 127	hsa-miR-574-3p	CACGCUCAUGCACACACCCACA
SEQ ID NO: 128	hsa-miR-1262	AUGGGUGAAUUUGUAGAAGGAU
SEQ ID NO: 129	hsa-miR-1537	AAAACCGUCUAGUUACAGUUGU
SEQ ID NO: 130	hsa-miR-298	AGCAGAAGCAGGGAGGUUCUCCA
SEQ ID NO: 131	hsa-miR-582-3p	UAACUGGUUGAACAACUGAACCC
SEQ ID NO: 132	hsa-miR-29b-2*	CUGGUUUCACAUGGUGGCUUAG
SEQ ID NO: 133	hsa-miR-548a-3p	CAAAACUGGCAAUUACUUUUGC
SEQ ID NO: 134	hsa-miR-411*	UAUGUAACACGGUCCACUAACC
SEQ ID NO: 135	hsa-miR-7-1*	CAACAAAUCACAGUCUGCCAUA
SEQ ID NO: 136	hsa-miR-520a-3p	AAAGUGCUUCCCUUUGGACUGU
SEQ ID NO: 137	hsa-miR-920	GGGGAGCUGUGGAAGCAGUA
SEQ ID NO: 138	hsa-miR-122*	AACGCCAUUAUCACACUAAUA
SEQ ID NO: 139	hsa-miR-615-3p	UCCGAGCCUGGGUCUCCCUCUU
SEQ ID NO: 140	hsa-miR-744	UGCGGGGCUAGGGCUAACAGCA
SEQ ID NO: 141	hsa-miR-875-5p	UAUACCUCAGUUUUUAUCAGGUG
SEQ ID NO: 142	hsa-miR-454*	ACCCUAUCAUAUUGUCUCUGC
SEQ ID NO: 143	hsa-miR-188-5p	CAUCCCUUGCAUGGUGGAGGG
SEQ ID NO: 144	hsa-miR-22*	AGUUCUUCAGUGGCAAGCUUUA
SEQ ID NO: 145	hsa-miR-125a-5p	UCCCUGAGACCCUUUAACUGUGA
SEQ ID NO: 146	hsa-let-7f-2*	CUAUACAGUCUACUGUCUUCC
SEQ ID NO: 147	hsa-miR-483-3p	UCACUCCUCUCCUCCGUCUU
SEQ ID NO: 148	hsa-miR-1304	UUUGAGGCUACAGUGAGAUGUG
SEQ ID NO: 149	hsa-miR-545*	UCAGUAAAUGUUUAUAGAUGA
SEQ ID NO: 150	hsa-miR-1254	AGCCUGGAAGCUGGAGCCUGCAGU
SEQ ID NO: 151	hsa-miR-92a-1*	AGGUUGGGAUCGGUUGCAAUGCU
SEQ ID NO: 152	hsa-miR-744*	CUGUUGCCACUAACCUCAACCU
SEQ ID NO: 153	hsa-miR-518d-5p	CUCUAGAGGGAAGCACUUUCUG
SEQ ID NO: 154	hsa-miR-26a	UUCAAGUAAUCCAGGAUAGGCU
SEQ ID NO: 155	hsa-miR-484	UCAGGCUCAGUCCCCUCCGAU

EP 2 865 765 A1

SEQ ID NO: 156	hsa-miR-217	UACUGCAUCAGGAACUGAUUGGA
SEQ ID NO: 157	hsa-miR-566	GGGCGCCUGUGAUCCCAAC
SEQ ID NO: 158	hsa-miR-515-5p	UUCUCCAAAAGAAAGCACUUUCUG
SEQ ID NO: 159	hsa-miR-126*	CAUUAUUACUUUUGGUACGCG
SEQ ID NO: 160	hsa-miR-200a	UAACACUGUCUGGUAACGAUGU
SEQ ID NO: 161	hsa-miR-302b*	ACUUUAACAUGGAAGUGCUUUC
SEQ ID NO: 162	hsa-miR-142-5p	CAUAAAGUAGAAAGCACUACU
SEQ ID NO: 163	hsa-miR-519e*	UUCUCCAAAAGGGAGCACUUUC
SEQ ID NO: 164	hsa-miR-512-5p	CACUCAGCCUUGAGGGCACUUUC
SEQ ID NO: 165	hsa-miR-101	UACAGUACUGUGAUACUGAA
SEQ ID NO: 166	hsa-miR-489	GUGACAUACAUAUACGGCAGC
SEQ ID NO: 167	hsa-miR-627	GUGAGUCUCUAAGAAAAGAGGA
SEQ ID NO: 168	hsa-let-7g	UGAGGUAGUAGUUUGUACAGUU
SEQ ID NO: 169	hsa-miR-324-3p	ACUGCCCCAGGUGCUGCUGG
SEQ ID NO: 170	hsa-miR-568	AUGUAUAAAUGUAUACACAC
SEQ ID NO: 171	hsa-miR-646	AAGCAGCUGCCUCUGAGGC
SEQ ID NO: 172	hsa-miR-27a	UUCACAGUGGCUAAGUUCGCG
SEQ ID NO: 173	hsa-miR-591	AGACCAUGGGUUCUCAUUGU
SEQ ID NO: 174	hsa-miR-636	UGUGCUUGCUCGUCCCGCCCGCA
SEQ ID NO: 175	hsa-miR-126	UCGUACCGUGAGUAAUAAUGCG
SEQ ID NO: 176	hsa-miR-26b	UUCAAGUAAUUCAGGAUAGGU
SEQ ID NO: 177	hsa-miR-621	GGCUAGCAACAGCGCUUACCU
SEQ ID NO: 178	hsa-miR-598	UACGUCAUCGUUGUCAUCGUCA
SEQ ID NO: 179	hsa-miR-603	CACACACUGCAAUUACUUUUGC
SEQ ID NO: 180	hsa-miR-214	ACAGCAGGCACAGACAGGCAGU
SEQ ID NO: 181	hsa-miR-145	GUCCAGUUUUCGAGGAAUCCCU
SEQ ID NO: 182	hsa-miR-155	UUAAUGCUAAUCGUGAUAGGGGU
SEQ ID NO: 183	hsa-miR-452*	CUCAUCUGCAAAGAAGUAAGUG
SEQ ID NO: 184	hsa-miR-492	AGGACCUGCGGGACAAGAUUCUU
SEQ ID NO: 185	hsa-miR-221	AGCUACAUUGUCUGCUGGGUUUC
SEQ ID NO: 186	hsa-miR-16	UAGCAGCACGUAAAUUUGGCG
SEQ ID NO: 187	hsa-miR-222	AGCUACAUCUGGCUACUGGGU
SEQ ID NO: 188	hsa-miR-302b	UAAGUGCUUCCAUGUUUUAGUAG
SEQ ID NO: 189	hsa-miR-564	AGGCACGGUGUCAGCAGGC
SEQ ID NO: 190	hsa-let-7d	AGAGGUAGUAGGUUGCAUAGUU
SEQ ID NO: 191	hsa-miR-596	AAGCCUGCCCGGCUCCUCGGG
SEQ ID NO: 192	hsa-miR-33b	GUGCAUUGCUGUUGCAUUGC
SEQ ID NO: 193	hsa-miR-422a	ACUGGACUUAGGGUCAGAAGGC
SEQ ID NO: 194	hsa-miR-510	UACUCAGGAGAGUGGCAAUCAC
SEQ ID NO: 195	hsa-miR-142-3p	UGUAGUGUUUCCUACUUUAUGGA
SEQ ID NO: 196	hsa-miR-487b	AAUCGUACAGGGUCAUCCACUU
SEQ ID NO: 197	hsa-miR-153	UUGCAUAGUCACAAAAGUGAUC
SEQ ID NO: 198	hsa-miR-143	UGAGAUGAAGCACUGUAGCUC
SEQ ID NO: 199	hsa-miR-497	CAGCAGCACACUGUGGUUUUGU
SEQ ID NO: 200	hsa-miR-554	GCUAGUCCUGACUCAGCCAGU
SEQ ID NO: 201	hsa-miR-514	AUUGACACUUCUGUGAGUAGA
SEQ ID NO: 202	hsa-miR-375	UUUGUUCGUUCGGCUCGCGUGA
SEQ ID NO: 203	hsa-miR-425	AAUGACACGAUCACUCCCGUUGA
SEQ ID NO: 204	hsa-miR-549	UGACAACUAUGGAUGAGCUCU
SEQ ID NO: 205	hsa-miR-521	AACGCACUCCCUUUAGAGUGU
SEQ ID NO: 206	hsa-miR-600	ACUUACAGACAAGAGCCUUGCUC
SEQ ID NO: 207	hsa-miR-32	UAUUGCACAUUACUAAGUUGCA
SEQ ID NO: 208	hsa-miR-520g	ACAAAGUGCUUCCCUUUAGAGUGU

EP 2 865 765 A1

SEQ ID NO: 209	hsa-miR-183	UAUGGCACUGGUAGAAUUCACU
SEQ ID NO: 210	hsa-miR-23b	AUCACAUUGCCAGGGAUUACC
SEQ ID NO: 211	hsa-miR-203	GUGAAAUGUUUAGGACCACUAG
SEQ ID NO: 212	hsa-miR-10a	UACCCUGUAGAUCCGAAUUUGUG
SEQ ID NO: 213	hsa-miR-346	UGUCUGCCCGCAUGCCUGCCUCU
SEQ ID NO: 214	hsa-miR-200a*	CAUCUUACCGGACAGUGCUGGA
SEQ ID NO: 215	hsa-miR-409-5p	AGGUUACCCGAGCAACUUUGCAU
SEQ ID NO: 216	hsa-miR-658	GGCGGAGGGAAGUAGGUCCGUUGU
SEQ ID NO: 217	hsa-miR-148b	UCAGUGCAUCACAGAACUUUGU
SEQ ID NO: 218	hsa-miR-363*	CGGGUGGAUCACGAUGCAAUUU
SEQ ID NO: 219	hsa-miR-34a	UGGCAGUGUCUUAGCUGGUUGU
SEQ ID NO: 220	hsa-miR-376a*	GUAGAUUCUCCUUCUAUGAGUA
SEQ ID NO: 221	hsa-miR-609	AGGGUGUUUCUCUCAUCUCU
SEQ ID NO: 222	hsa-miR-299-3p	UAUGUGGGAUGGUAACCGCUU
SEQ ID NO: 223	hsa-miR-542-5p	UCGGGGAUCAUCAUGUCACGAGA
SEQ ID NO: 224	hsa-miR-550	AGUGCCUGAGGGAGUAAGAGCCC
SEQ ID NO: 225	hsa-miR-575	GAGCCAGUUGGACAGGAGC
SEQ ID NO: 226	hsa-miR-629	UGGGUUUACGUUGGGAGAACU
SEQ ID NO: 227	hsa-miR-22	AAGCUGCCAGUUGAAGAACUGU
SEQ ID NO: 228	hsa-miR-149	UCUGGCUCGUGUCUUCACUCCC
SEQ ID NO: 229	hsa-miR-520h	ACAAAGUGCUUCCCUUUAGAGU
SEQ ID NO: 230	hsa-miR-451	AAACCGUUACCAUUACUGAGUU
SEQ ID NO: 231	hsa-miR-93	CAAAGUGCUGUUCGUGCAGGUAG
SEQ ID NO: 232	hsa-miR-624	CACAAGGUUUUGGUUUUACCU
SEQ ID NO: 233	hsa-miR-433	AUCAUGAUGGGCUCUCGGUGU
SEQ ID NO: 234	hsa-miR-498	UUUCAAGCCAGGGGGCGUUUUUC
SEQ ID NO: 235	hsa-miR-518b	CAAAGCGCUCUUUUUAGAGGU
SEQ ID NO: 236	hsa-miR-448	UUGCAUAUGUAGGAUGUCCCAU
SEQ ID NO: 237	hsa-miR-639	AUCGCGCGGUUGCGAGCGCUGU
SEQ ID NO: 238	hsa-miR-21	UAGCUUAUCAGACUGAUGUUGA
SEQ ID NO: 239	hsa-miR-1	UGGAAUGUAAAGAAGUAUGUAU
SEQ ID NO: 240	hsa-miR-223	UGUCAGUUUGUCAAUACCCCA
SEQ ID NO: 241	hsa-miR-30c	UGUAAACAUCUACACUCUCAGC
SEQ ID NO: 242	hsa-let-7i	UGAGGUAGUAGUUUGUGCUGUU
SEQ ID NO: 243	hsa-miR-151-5p	UCGAGGAGCUCACAGUCUAGU
SEQ ID NO: 244	hsa-miR-874	CUGCCCUGGCCCGAGGGACCGA
SEQ ID NO: 245	hsa-miR-106a	AAAAGUGCUUACAGUGCAGGUAG
SEQ ID NO: 246	hsa-miR-20a	UAAAGUGCUUUAUAGUGCAGGUAG
SEQ ID NO: 247	hsa-miR-148a	UCAGUGCACUACAGAACUUUGU
SEQ ID NO: 248	hsa-let-7b	UGAGGUAGUAGGUUGUGUGGUU
SEQ ID NO: 249	hsa-miR-33b*	CAGUGCCUCGGCAGUGCAGCCC
SEQ ID NO: 250	hsa-miR-374a	UUUAUUAACAACCUGAUAAAGUG
SEQ ID NO: 251	hsa-miR-182	UUUGGCAAUGGUAGAACUCACACU
SEQ ID NO: 252	hsa-miR-497*	CAAACCACACUGUGGUGUUAGA
SEQ ID NO: 253	hsa-miR-345	GCUGACUCCUAGUCCAGGGCUC
SEQ ID NO: 254	hsa-miR-323-3p	CACAUUACACGGUCGACCUCU
SEQ ID NO: 255	hsa-miR-193a-3p	AACUGGCCUACAAAGUCCCAGU
SEQ ID NO: 256	hsa-miR-134	UGUGACUGGUUGACCAGAGGGG
SEQ ID NO: 257	hsa-miR-663b	GGUGGCCCGGCCGUGCCUGAGG
SEQ ID NO: 258	hsa-miR-499-3p	AACAUCACAGCAAGUCUGUGCU
SEQ ID NO: 259	hsa-miR-631	AGACCUGGCCAGACCUCAGC
SEQ ID NO: 260	hsa-miR-544	AUUCUGCAUUUUUAGCAAGUUC
SEQ ID NO: 261	hsa-miR-200b*	CAUCUUACUGGGCAGCAUUGGA

EP 2 865 765 A1

SEQ ID NO: 262	hsa-miR-326	CCUCUGGGCCCUUCCUCCAG
SEQ ID NO: 263	hsa-miR-409-3p	GAAUGUUGCUCGGUGAACCCCU
SEQ ID NO: 264	hsa-miR-513a-5p	UUCACAGGGAGGUGUCAU
SEQ ID NO: 265	hsa-miR-129-5p	CUUUUUGCGGUCUGGGCUUGC
SEQ ID NO: 266	hsa-miR-615-5p	GGGGGUCCCCGGUGCUCGGAUC
SEQ ID NO: 267	hsa-miR-193b	AACUGGCCCUCAAAGUCCCGCU
SEQ ID NO: 268	hsa-miR-877*	UCCUCUUCUCCCUCCUCCAG
SEQ ID NO: 269	hsa-miR-105	UCAAUUGCUCAGACUCCUGUGGU
SEQ ID NO: 270	hsa-miR-296-3p	GAGGGUUGGGUGGAGGCUCUCC
SEQ ID NO: 271	hsa-miR-27a*	AGGGCUUAGCUGCUUGUGAGCA
SEQ ID NO: 272	hsa-miR-99b*	CAAGCUCGUGUCUGUGGGUCCG
SEQ ID NO: 273	hsa-miR-194*	CCAGUGGGGCUGCUGUUAUCUG
SEQ ID NO: 274	hsa-miR-653	GUGUUGAAACAAUCUCUACUG
SEQ ID NO: 275	hsa-miR-608	AGGGGUGGUGUUGGGACAGCUCCGU
SEQ ID NO: 276	hsa-miR-337-5p	GAACGGCUUCAUACAGGAGUU
SEQ ID NO: 277	hsa-miR-1207-3p	UCAGCUGGCCCUCAUUUC
SEQ ID NO: 278	hsa-miR-579	UUCAUUUGGUUAAACCGCGAUU
SEQ ID NO: 279	hsa-miR-323-5p	AGGUGGUCCGUGGCGCGUUCGC
SEQ ID NO: 280	hsa-miR-634	AACCAGCACCCCAACUUUGGAC
SEQ ID NO: 281	hsa-miR-144*	GGUAUUAUUAUUAUACUGUAAG
SEQ ID NO: 282	hsa-miR-519d	CAAAGUGCCUCCCUUAGAGUG
SEQ ID NO: 283	hsa-miR-191*	GCUGCGCUUGGAUUUCGUCCCC

Figure 13

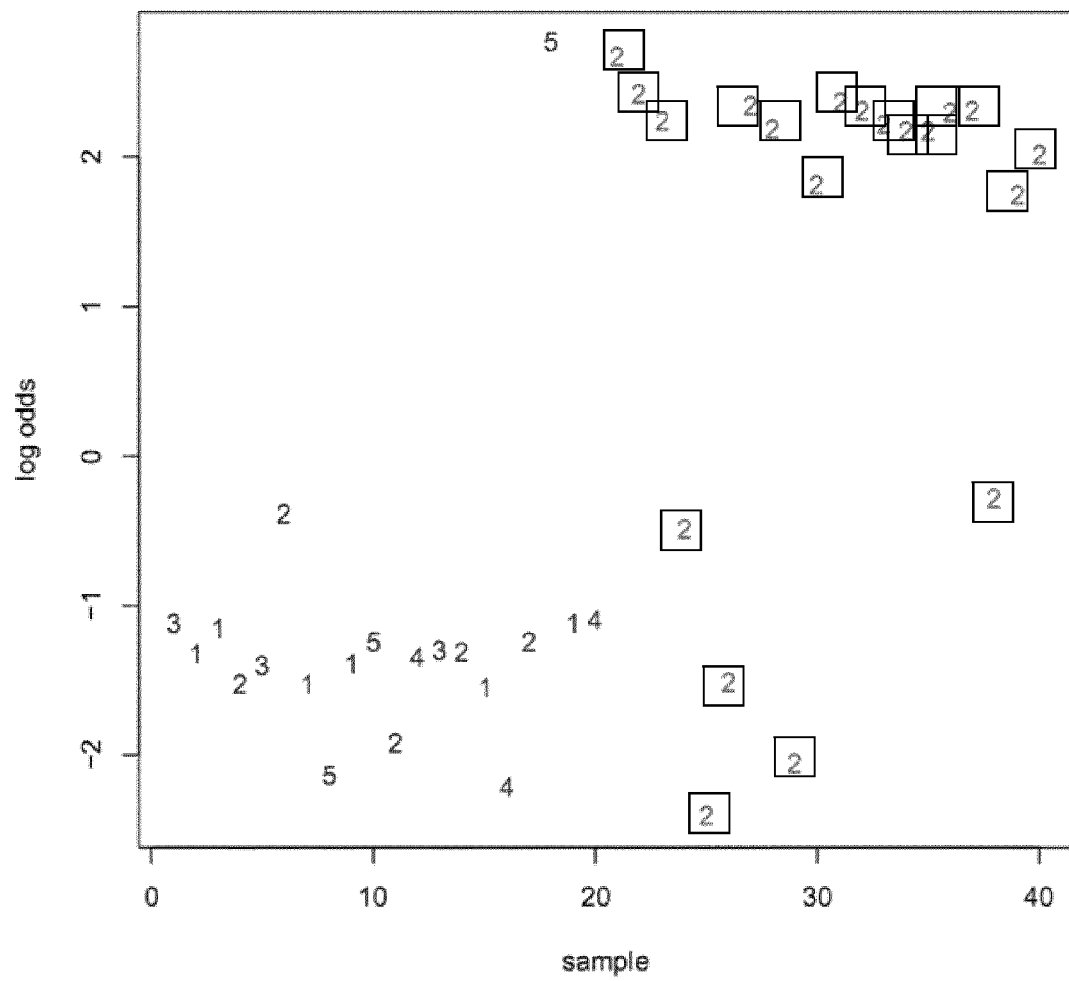


Figure 14

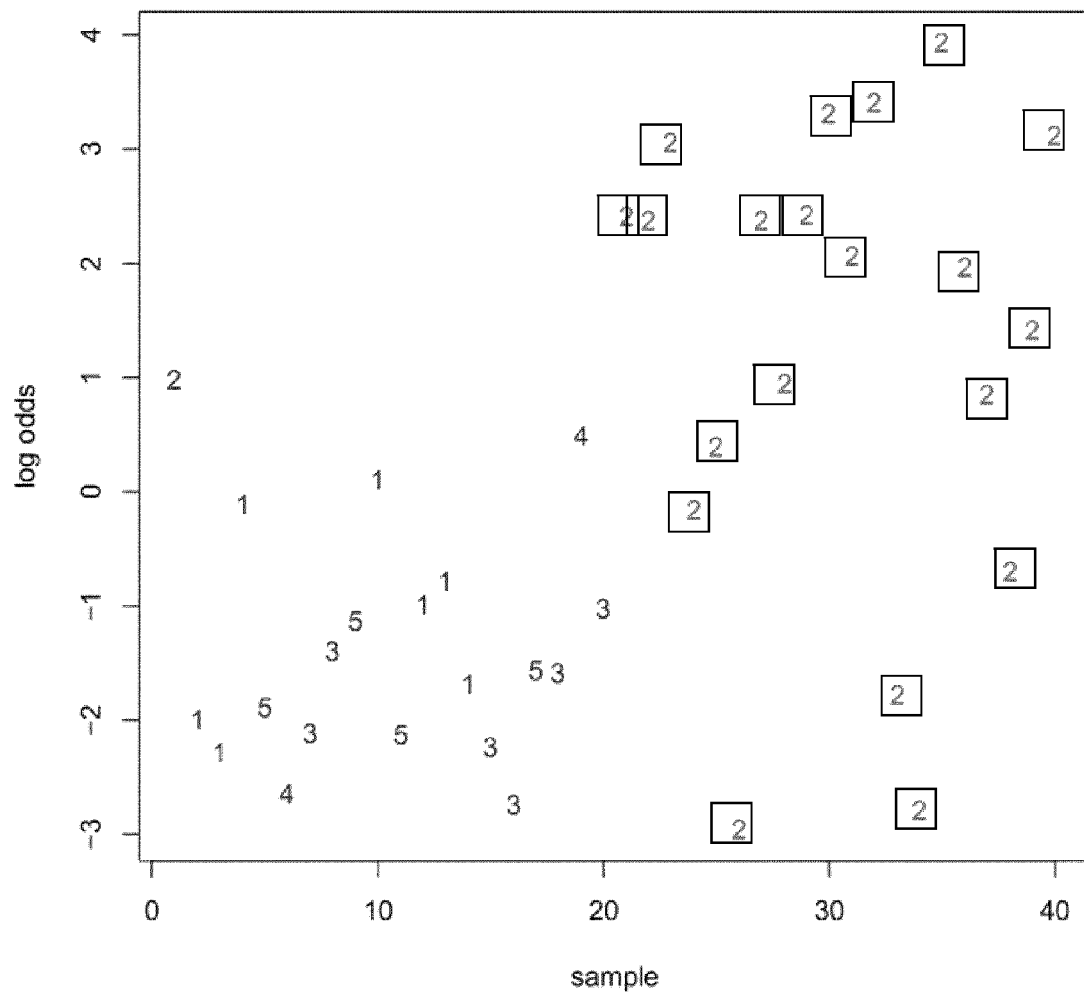


Figure 15

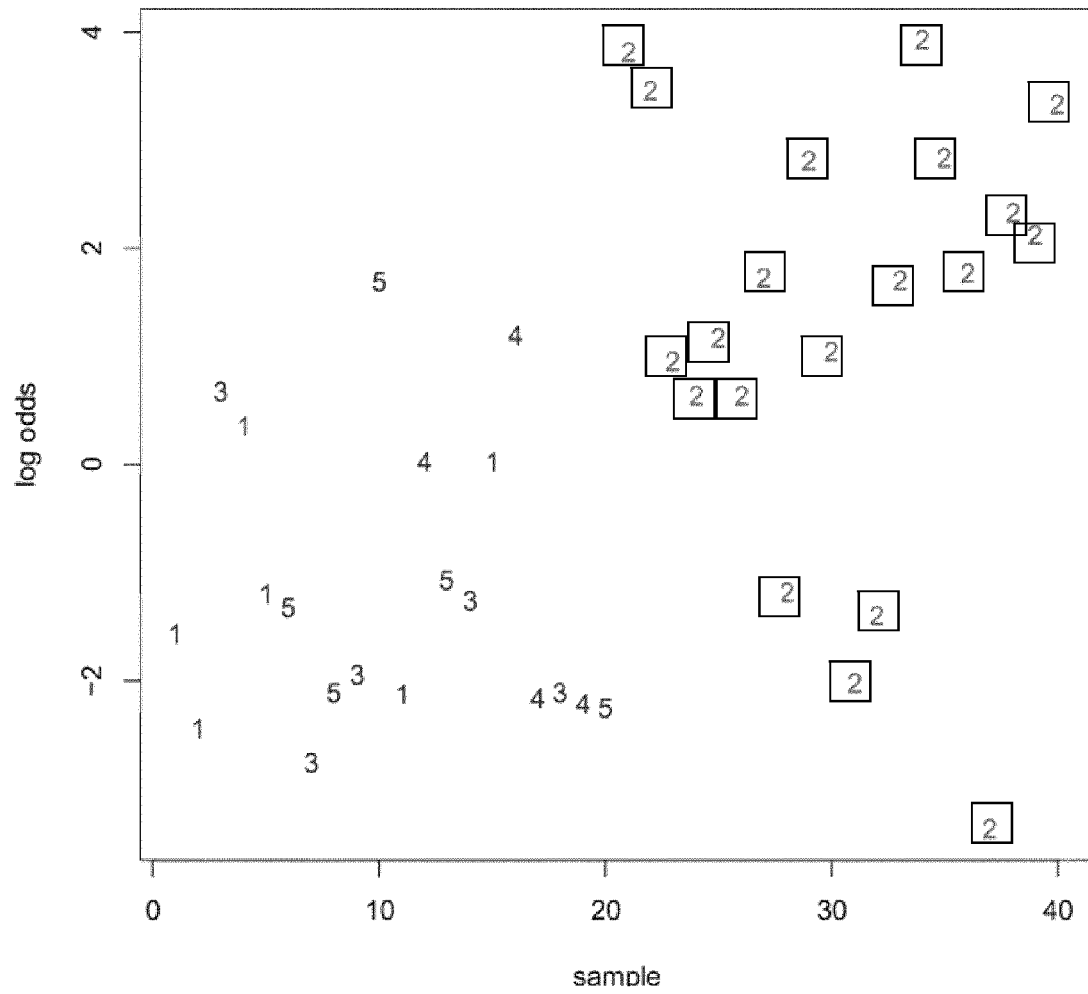


Figure 16

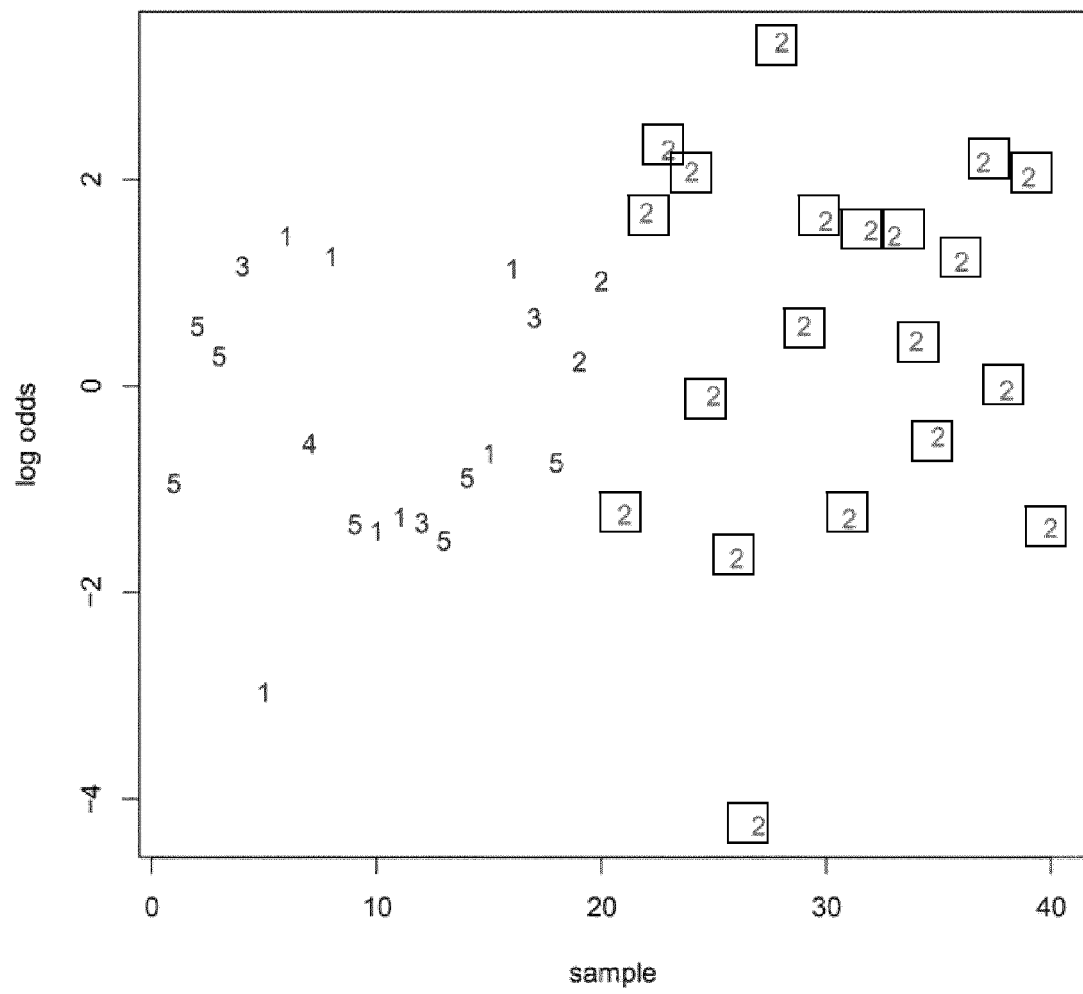


Figure 17

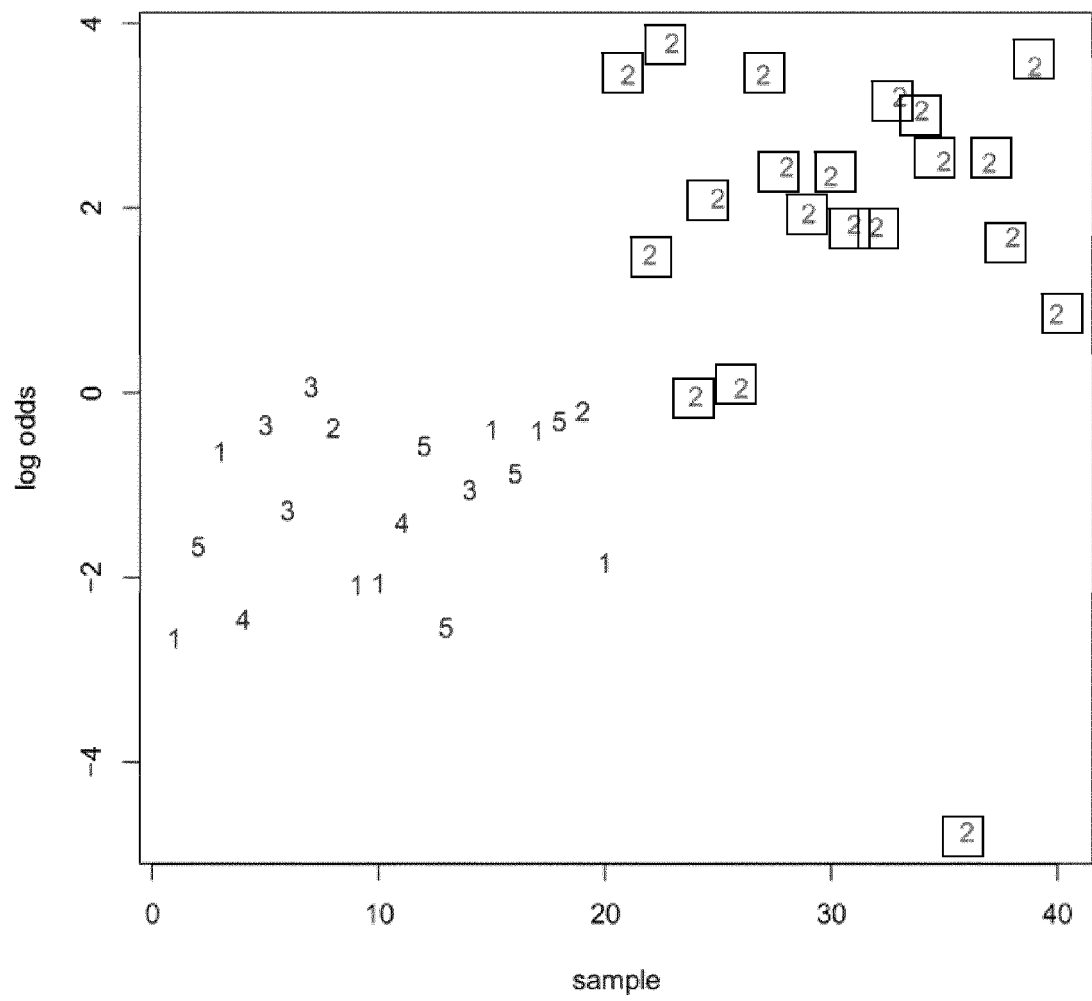


Figure 18

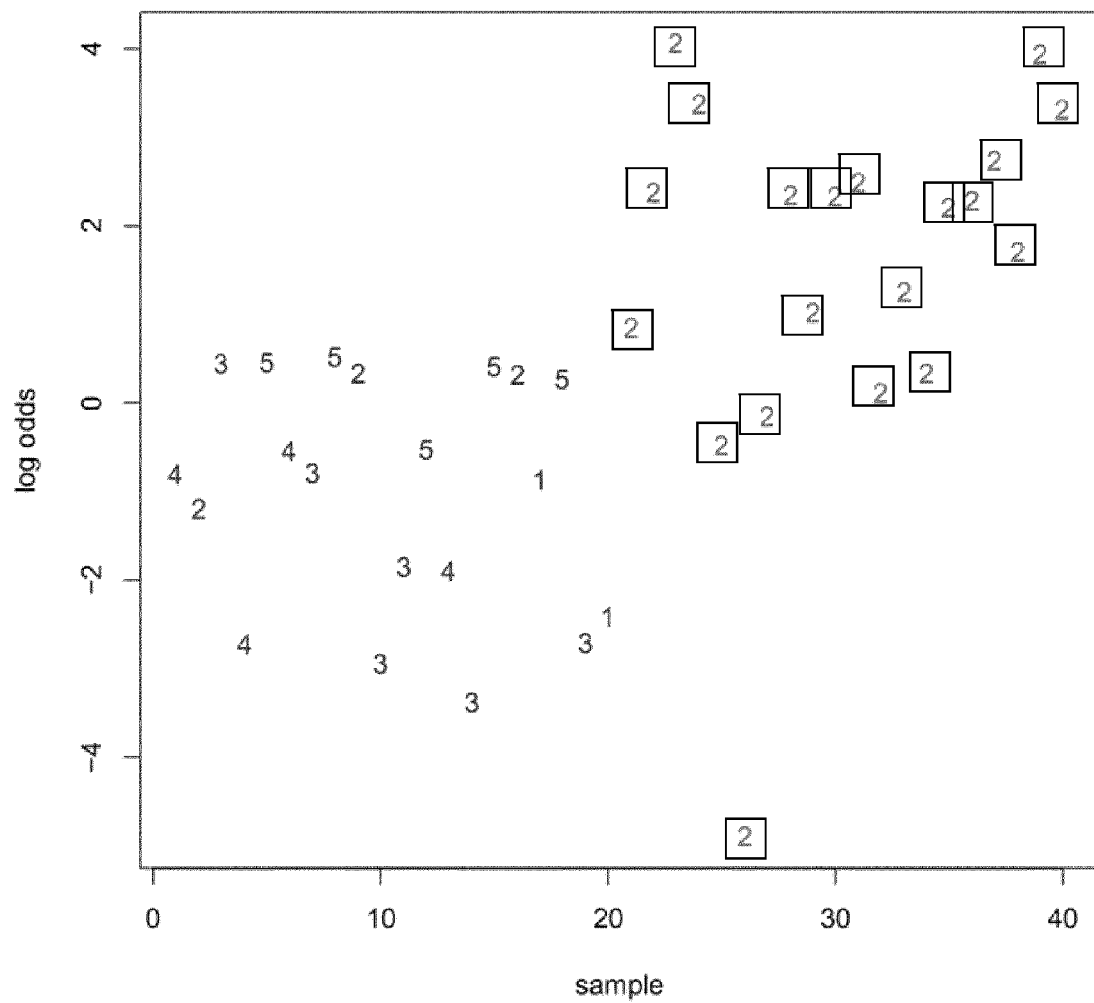


Figure 19

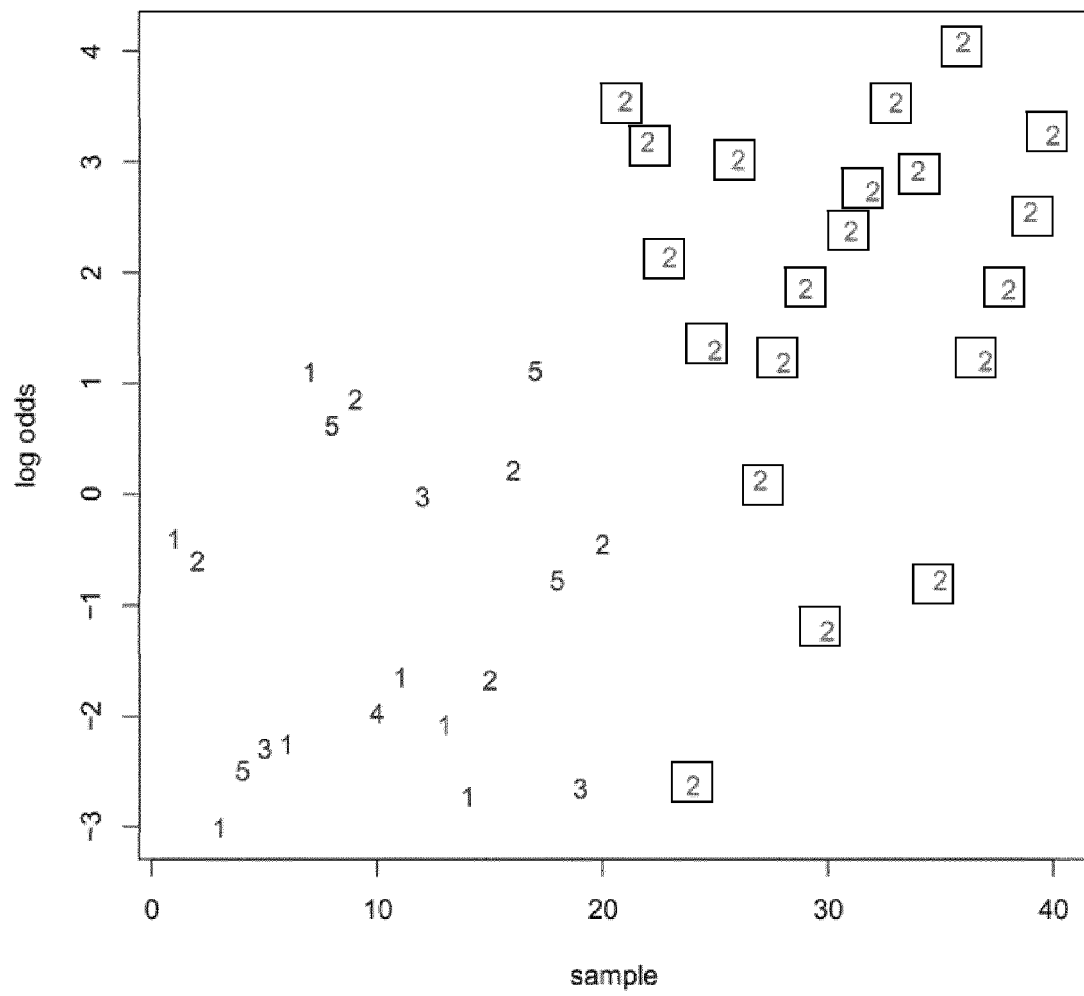


Figure 20

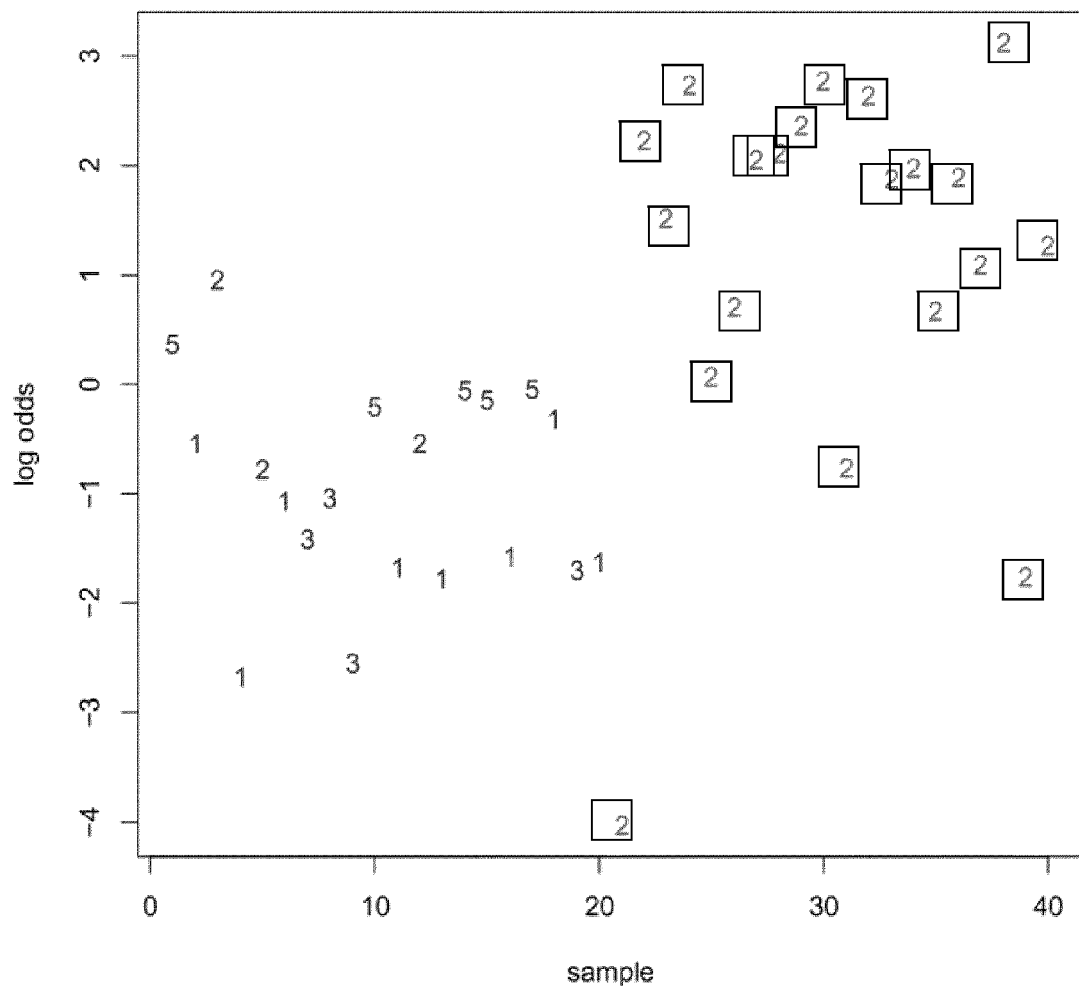


Figure 21

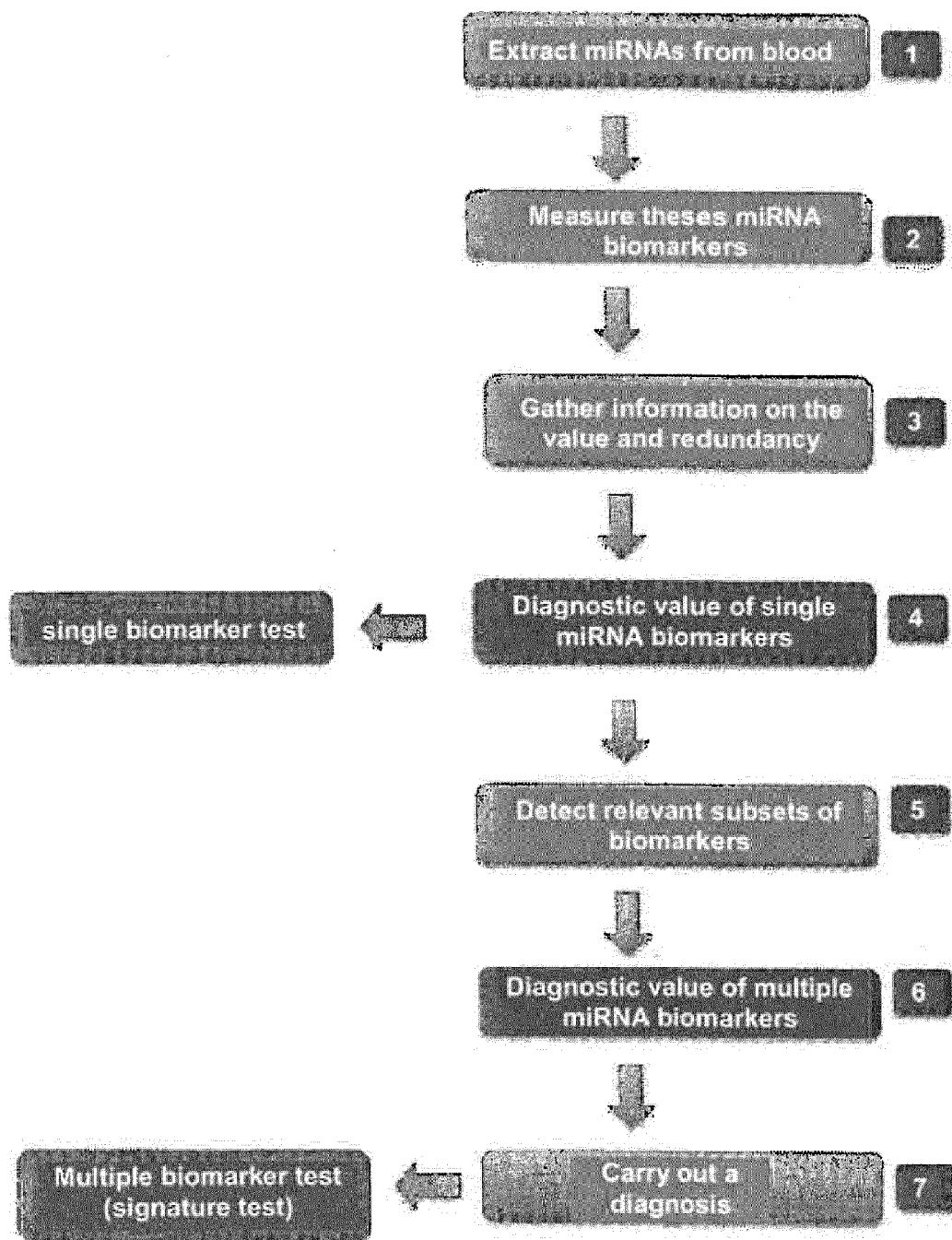
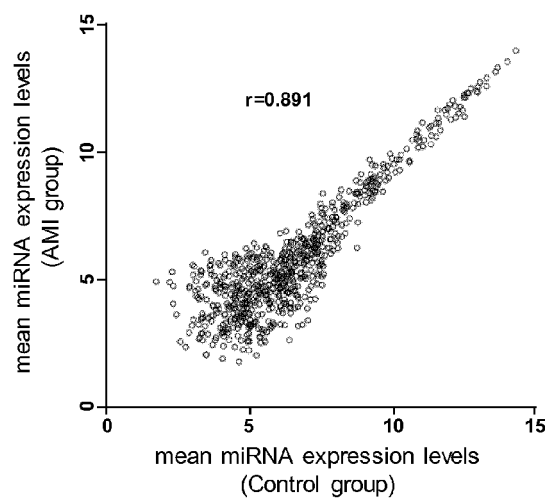


Figure 22

A



B

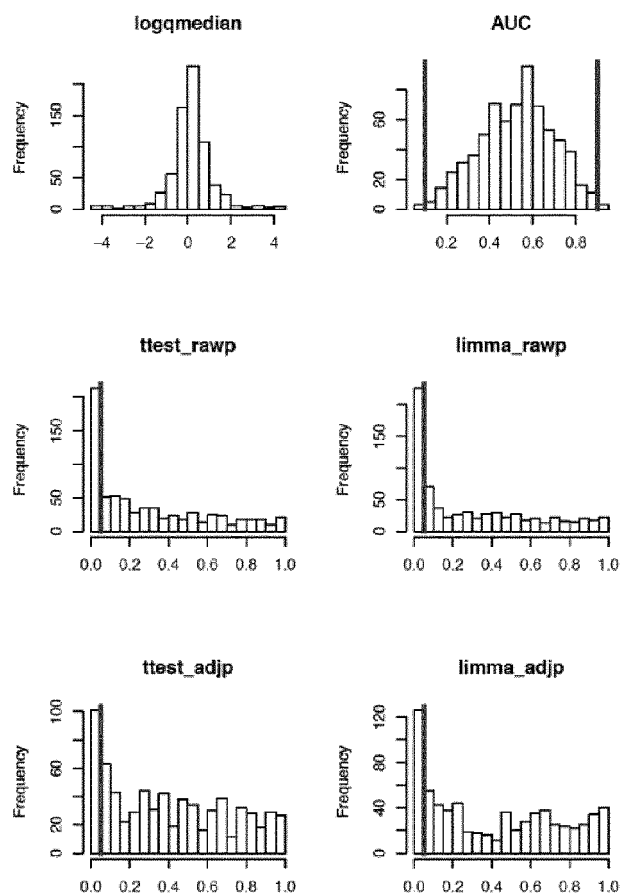


Figure 23

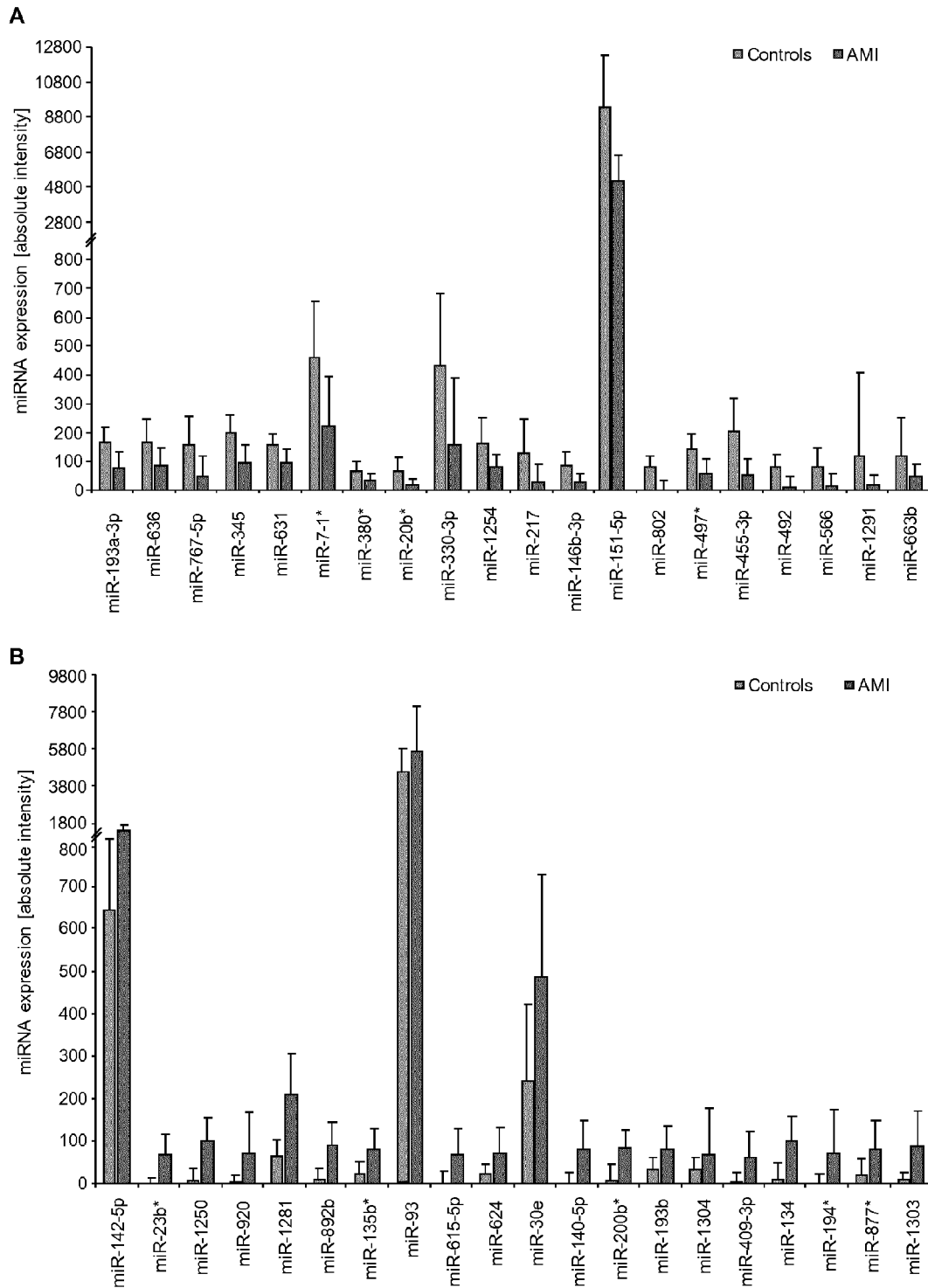


Figure 24

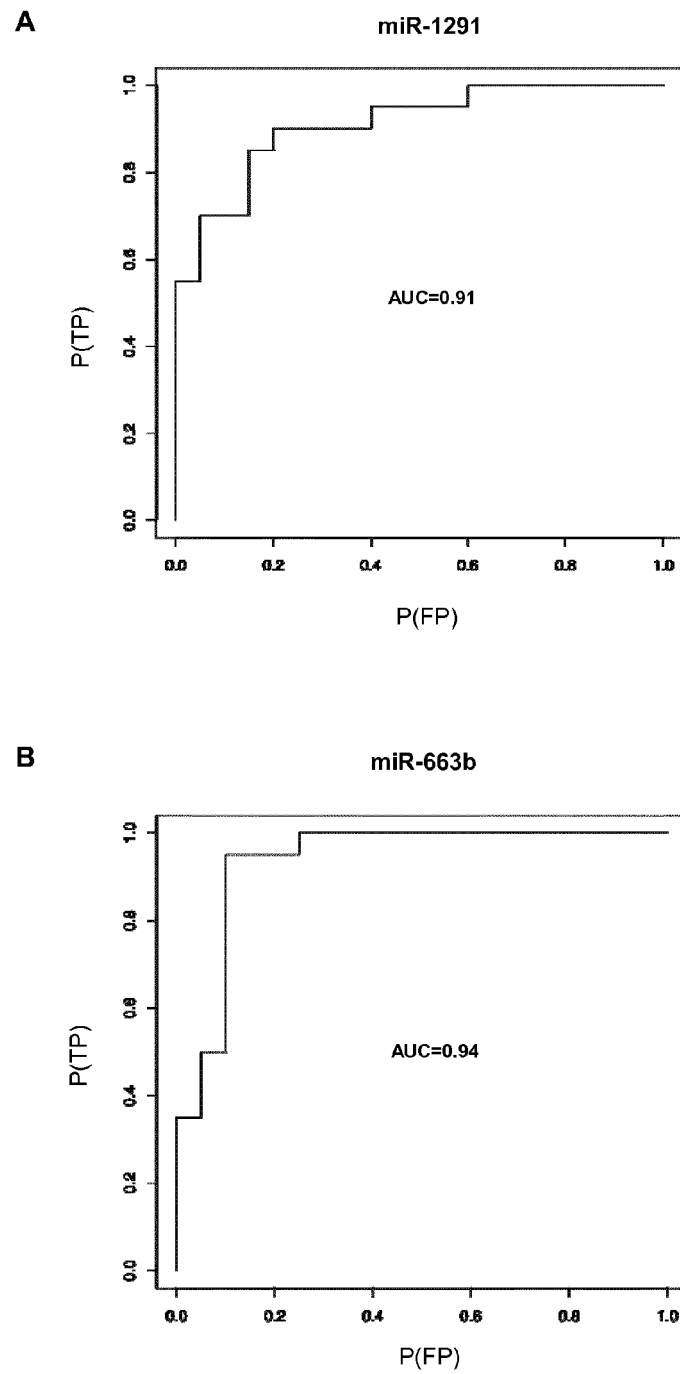


Figure 25

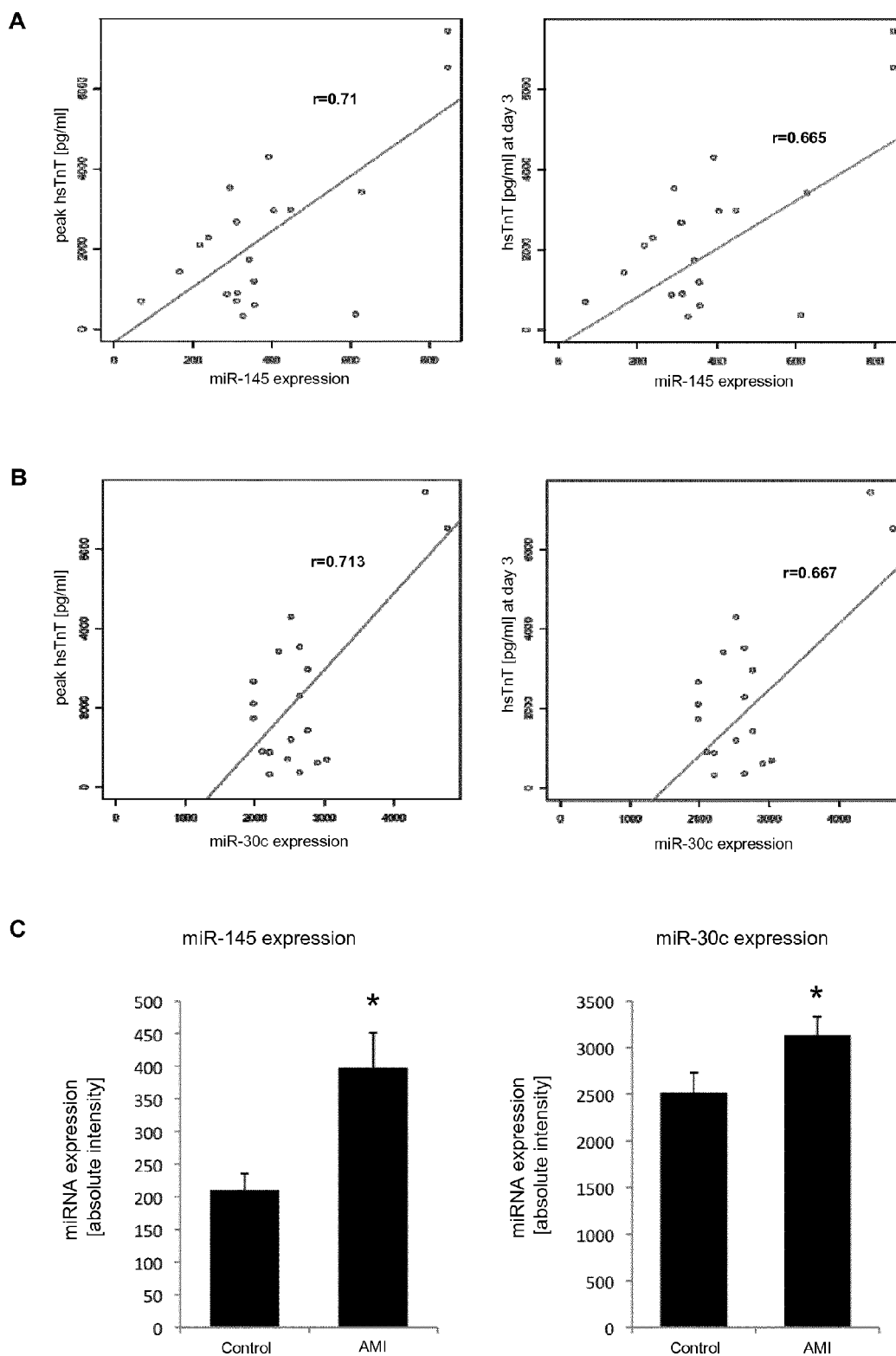


Figure 26

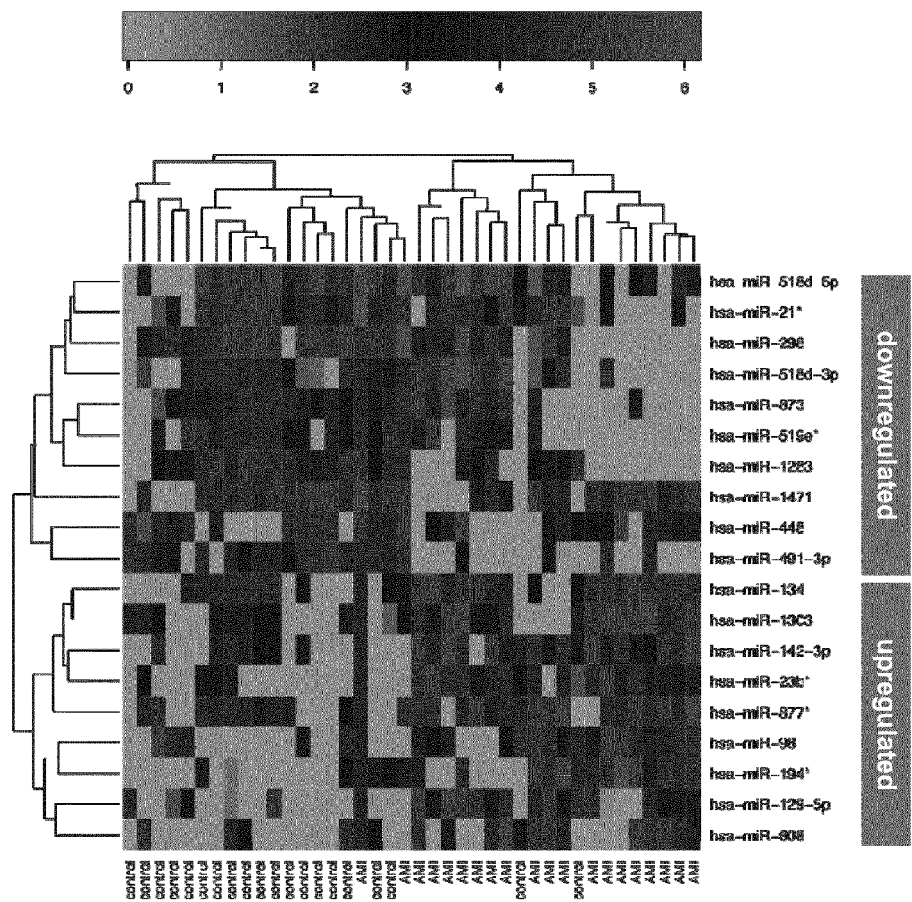


Figure 27

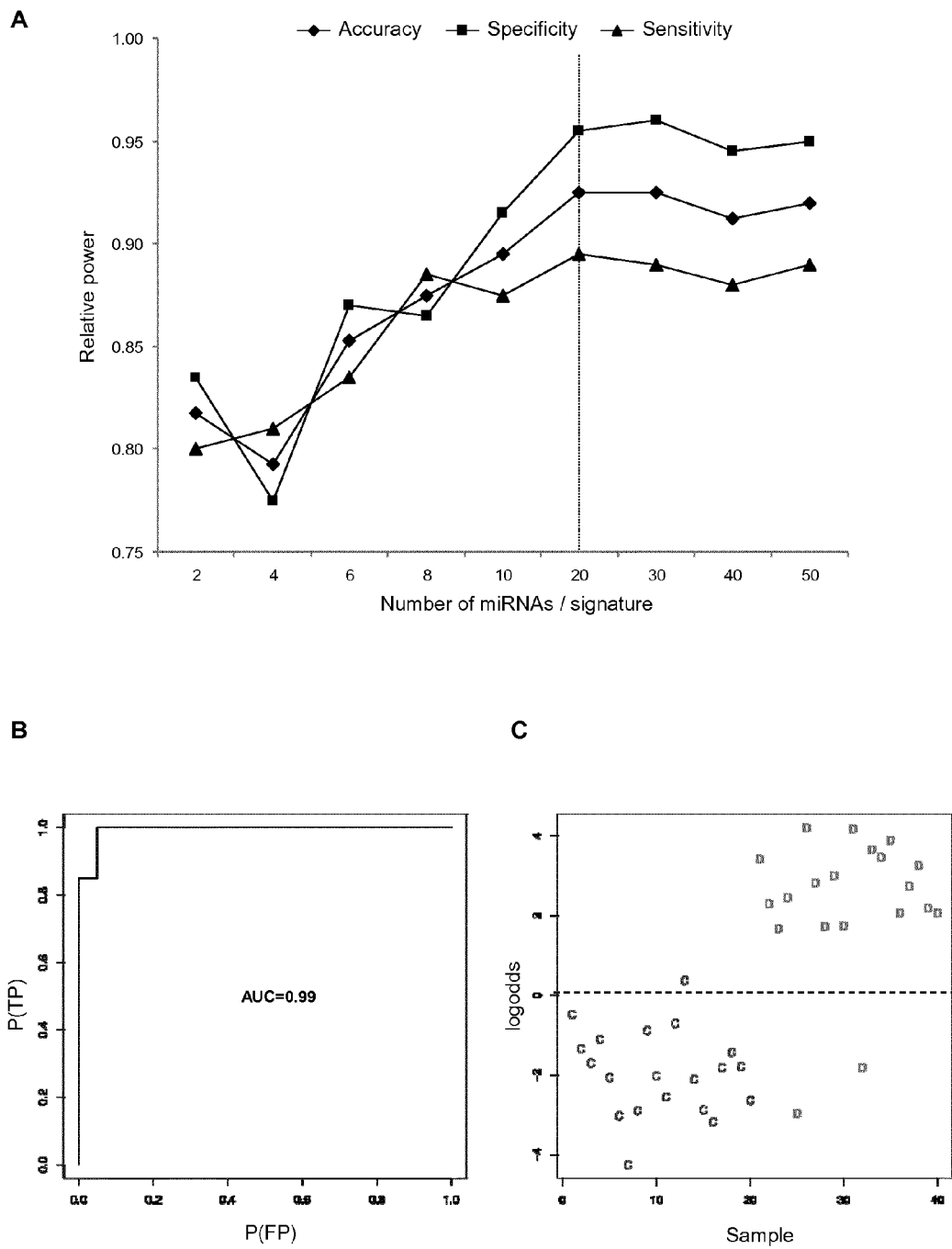


Figure 28

Set No.	SEQ-ID NO:	miRNAs	Acc	Spec	Sens
1	SEQ ID NO: 162, 16	hsa-miR-142-5p, hsa-miR-455-3p	97.5 %	100.0 %	95.0 %
2	SEQ ID NO: 150, 174	hsa-miR-1254, hsa-miR-636	96.8 %	95.2 %	98.4 %
3	SEQ ID NO: 243, 244	hsa-miR-151-5p, hsa-miR-874	94.8 %	89.6 %	100.0 %
4	SEQ ID NO: 243, 123	hsa-miR-151-5p, hsa-miR-146b-3p	94.6 %	89.2 %	100.0 %
5	SEQ ID NO: 24, 243	hsa-miR-330-3p, hsa-miR-151-5p	94.4 %	94.2 %	94.6 %
6	SEQ ID NO: 243, 16	hsa-miR-151-5p, hsa-miR-455-3p	94.3 %	89.8 %	98.8 %
7	SEQ ID NO: 234, 52	hsa-miR-498, hsa-miR-802	93.4 %	90.8 %	96.0 %
8	SEQ ID NO: 62, 52	hsa-miR-1281, hsa-miR-802	92.9 %	100.0 %	85.8 %
9	SEQ ID NO: 234, 62	hsa-miR-498, hsa-miR-1281	92.6 %	91.0 %	94.2 %
10	SEQ ID NO: 137, 162	hsa-miR-920, hsa-miR-142-5p	92.6 %	95.0 %	90.2 %
11	SEQ ID NO: 137, 243	hsa-miR-920, hsa-miR-151-5p	92.5 %	94.8 %	90.2 %
12	SEQ ID NO: 52, 62	hsa-miR-802, hsa-miR-1281	92.4 %	99.2 %	85.6 %
13	SEQ ID NO: 162, 252	hsa-miR-142-5p, hsa-miR-497*	92.3 %	90.6 %	94.0 %
14	SEQ ID NO: 243, 231	hsa-miR-151-5p, hsa-miR-93	92.3 %	93.0 %	91.6 %
15	SEQ ID NO: 62, 253	hsa-miR-1281, hsa-miR-345	92.2 %	94.4 %	90.0 %
16	SEQ ID NO: 15, 243	hsa-miR-892b, hsa-miR-151-5p	92.0 %	95.2 %	88.8 %
17	SEQ ID NO: 157, 137	hsa-miR-566, hsa-miR-920	92.0 %	94.8 %	89.2 %
18	SEQ ID NO: 243, 19	hsa-miR-151-5p, hsa-miR-767-5p	92.0 %	90.8 %	93.2 %
19	SEQ ID NO: 162, 24	hsa-miR-142-5p, hsa-miR-330-3p	91.8 %	88.8 %	94.8 %
20	SEQ ID NO: 62, 150	hsa-miR-1281, hsa-miR-1254	91.7 %	98.6 %	84.8 %
21	SEQ ID NO: 184, 162	hsa-miR-492, hsa-miR-142-5p	91.7 %	94.6 %	88.8 %
22	SEQ ID NO: 52, 68	hsa-miR-802, hsa-miR-23b*	91.6 %	98.0 %	85.2 %
23	SEQ ID NO: 68, 52	hsa-miR-23b*, hsa-miR-802	91.5 %	98.0 %	85.0 %
24	SEQ ID NO: 162, 184	hsa-miR-142-5p, hsa-miR-492	91.4 %	94.0 %	88.8 %
25	SEQ ID NO: 150, 257	hsa-miR-1254, hsa-miR-663b	91.4 %	95.0 %	87.8 %
26	SEQ ID NO: 234, 68	hsa-miR-498, hsa-miR-23b*	91.3 %	90.2 %	92.4 %
27	SEQ ID NO: 15, 22	hsa-miR-892b, hsa-miR-20b*	91.1 %	94.2 %	88.0 %
28	SEQ ID NO: 137, 52	hsa-miR-920, hsa-miR-802	91.1 %	97.0 %	85.2 %
29	SEQ ID NO: 162, 70	hsa-miR-142-5p, hsa-miR-1250	91.0 %	94.0 %	88.0 %
30	SEQ ID NO: 243, 62	hsa-miR-151-5p, hsa-miR-1281	90.9 %	94.8 %	87.0 %

EP 2 865 765 A1

			%	%	%
31	SEQ ID NO: 52, 184	hsa-miR-802, hsa-miR-492	90.7 %	99.2 %	82.2 %
32	SEQ ID NO: 162, 62	hsa-miR-142-5p, hsa-miR-1281	90.6 %	95.0 %	86.2 %
33	SEQ ID NO: 62, 243	hsa-miR-1281, hsa-miR-151-5p	90.6 %	94.6 %	86.6 %
34	SEQ ID NO: 184, 52	hsa-miR-492, hsa-miR-802	90.5 %	100.0 %	81.0 %
35	SEQ ID NO: 257, 162	hsa-miR-663b, hsa-miR-142-5p	90.3 %	90.8 %	89.8 %
36	SEQ ID NO: 68, 137	hsa-miR-23b*, hsa-miR-920	90.3 %	99.8 %	80.8 %
37	SEQ ID NO: 234, 252	hsa-miR-498, hsa-miR-497*	90.2 %	90.0 %	90.4 %
38	SEQ ID NO: 252, 184	hsa-miR-497*, hsa-miR-492	90.2 %	96.0 %	84.4 %
39	SEQ ID NO: 157, 184	hsa-miR-566, hsa-miR-492	90.2 %	99.8 %	80.6 %
40	SEQ ID NO: 52, 137	hsa-miR-802, hsa-miR-920	90.2 %	95.8 %	84.6 %
41	SEQ ID NO: 52, 16	hsa-miR-802, hsa-miR-455-3p	90.0 %	97.2 %	82.8 %
42	SEQ ID NO: 257, 234	hsa-miR-663b, hsa-miR-498	90.0 %	85.0 %	95.0 %
43	SEQ ID NO: 62, 95	hsa-miR-1281, hsa-miR-135b*	89.8 %	95.6 %	84.0 %
44	SEQ ID NO: 62, 123	hsa-miR-1281, hsa-miR-146b-3p	89.7 %	98.4 %	81.0 %
45	SEQ ID NO: 234, 184	hsa-miR-498, hsa-miR-492	89.6 %	85.2 %	94.0 %
46	SEQ ID NO: 253, 123	hsa-miR-345, hsa-miR-146b-3p	89.6 %	94.2 %	85.0 %
47	SEQ ID NO: 123, 156	hsa-miR-146b-3p, hsa-miR-217	89.5 %	99.4 %	79.6 %
48	SEQ ID NO: 257, 157	hsa-miR-663b, hsa-miR-566	89.4 %	95.0 %	83.8 %
49	SEQ ID NO: 243, 70	hsa-miR-151-5p, hsa-miR-1250	89.3 %	80.4 %	98.2 %
50	SEQ ID NO: 162, 157	hsa-miR-142-5p, hsa-miR-566	89.2 %	93.8 %	84.6 %
51	SEQ ID NO: 32, 252	hsa-miR-380*, hsa-miR-497*	89.2 %	89.6 %	88.8 %
52	SEQ ID NO: 157, 162	hsa-miR-566, hsa-miR-142-5p	89.1 %	93.2 %	85.0 %
53	SEQ ID NO: 95, 157	hsa-miR-135b*, hsa-miR-566	89.0 %	99.6 %	78.4 %
54	SEQ ID NO: 68, 252	hsa-miR-23b*, hsa-miR-497*	89.0 %	98.2 %	79.8 %
55	SEQ ID NO: 135, 19	hsa-miR-7-1*, hsa-miR-767-5p	88.8 %	83.4 %	94.2 %
56	SEQ ID NO: 244, 254	hsa-miR-874, hsa-miR-323-3p	88.6 %	81.6 %	95.6 %
57	SEQ ID NO: 150, 157	hsa-miR-1254, hsa-miR-566	88.5 %	92.8 %	84.2 %
58	SEQ ID NO: 162, 265	hsa-miR-142-5p, hsa-miR-129-5p	88.4 %	89.2 %	87.6 %
59	SEQ ID NO: 15, 62	hsa-miR-892b, hsa-miR-1281	88.3 %	96.6 %	80.0 %
60	SEQ ID NO: 68, 16	hsa-miR-23b*, hsa-miR-455-3p	88.1 %	96.4 %	79.8 %
61	SEQ ID NO: 62, 16	hsa-miR-1281, hsa-miR-455-3p	88.0 %	95.0 %	81.0 %

EP 2 865 765 A1

62	SEQ ID NO: 150, 253	hsa-miR-1254, hsa-miR-345	87.9 %	89.8 %	86.0 %
63	SEQ ID NO: 162, 135	hsa-miR-142-5p, hsa-miR-7-1*	87.9 %	88.2 %	87.6 %
64	SEQ ID NO: 266, 24	hsa-miR-615-5p, hsa-miR-330-3p	87.9 %	95.8 %	80.0 %
65	SEQ ID NO: 95, 269	hsa-miR-135b*, hsa-miR-105	87.9 %	90.0 %	85.8 %
66	SEQ ID NO: 184, 70	hsa-miR-492, hsa-miR-1250	87.8 %	90.2 %	85.4 %
67	SEQ ID NO: 162, 234	hsa-miR-142-5p, hsa-miR-498	87.7 %	85.4 %	90.0 %
68	SEQ ID NO: 253, 31	hsa-miR-345, hsa-miR-139-5p	87.7 %	90.4 %	85.0 %
69	SEQ ID NO: 252, 52	hsa-miR-497*, hsa-miR-802	87.5 %	100.0 %	75.0 %
70	SEQ ID NO: 269, 135	hsa-miR-105, hsa-miR-7-1*	87.5 %	95.0 %	80.0 %
71	SEQ ID NO: 52, 157	hsa-miR-802, hsa-miR-566	87.5 %	100.0 %	75.0 %
72	SEQ ID NO: 70, 266	hsa-miR-1250, hsa-miR-615-5p	87.5 %	94.6 %	80.4 %
73	SEQ ID NO: 252, 15	hsa-miR-497*, hsa-miR-892b	87.4 %	99.6 %	75.2 %
74	SEQ ID NO: 265, 257	hsa-miR-129-5p, hsa-miR-663b	87.4 %	86.4 %	88.4 %
75	SEQ ID NO: 116, 62	hsa-miR-339-3p, hsa-miR-1281	87.1 %	93.2 %	81.0 %
76	SEQ ID NO: 68, 157	hsa-miR-23b*, hsa-miR-566	87.0 %	95.2 %	78.8 %
77	SEQ ID NO: 157, 234	hsa-miR-566, hsa-miR-498	86.9 %	83.6 %	90.2 %
78	SEQ ID NO: 232, 71	hsa-miR-624, hsa-miR-30e	86.9 %	94.4 %	79.4 %
79	SEQ ID NO: 15, 95	hsa-miR-892b, hsa-miR-135b*	86.8 %	99.8 %	73.8 %
80	SEQ ID NO: 52, 15	hsa-miR-802, hsa-miR-892b	86.7 %	100.0 %	73.4 %
81	SEQ ID NO: 157, 68	hsa-miR-566, hsa-miR-23b*	86.7 %	95.0 %	78.4 %
82	SEQ ID NO: 257, 95	hsa-miR-663b, hsa-miR-135b*	86.5 %	88.8 %	84.2 %
83	SEQ ID NO: 184, 243	hsa-miR-492, hsa-miR-151-5p	86.4 %	87.4 %	85.4 %
84	SEQ ID NO: 16, 253	hsa-miR-455-3p, hsa-miR-345	86.3 %	87.0 %	85.6 %
85	SEQ ID NO: 234, 157	hsa-miR-498, hsa-miR-566	86.3 %	82.6 %	90.0 %
86	SEQ ID NO: 62, 184	hsa-miR-1281, hsa-miR-492	86.1 %	91.8 %	80.4 %
87	SEQ ID NO: 157, 253	hsa-miR-566, hsa-miR-345	86.1 %	89.6 %	82.6 %
88	SEQ ID NO: 253, 174	hsa-miR-345, hsa-miR-636	86.1 %	84.4 %	87.8 %
89	SEQ ID NO: 162, 71	hsa-miR-142-5p, hsa-miR-30e	86.0 %	93.4 %	78.6 %
90	SEQ ID NO: 162, 266	hsa-miR-142-5p, hsa-miR-615-5p	85.7 %	79.2 %	92.2 %
91	SEQ ID NO: 123, 269	hsa-miR-146b-3p, hsa-miR-105	85.7 %	90.4 %	81.0 %
92	SEQ ID NO: 157, 15	hsa-miR-566, hsa-miR-892b	85.6 %	91.4 %	79.8 %
93	SEQ ID NO: 167, 243	hsa-miR-627, hsa-miR-151-5p	85.6 %	83.2 %	88.0 %

EP 2 865 765 A1

			%	%	%
94	SEQ ID NO: 184, 16	hsa-miR-492, hsa-miR-455-3p	85.6 %	87.0 %	84.2 %
95	SEQ ID NO: 253, 15	hsa-miR-345, hsa-miR-892b	85.5 %	90.8 %	80.2 %
96	SEQ ID NO: 137, 70	hsa-miR-920, hsa-miR-1250	85.5 %	85.6 %	85.4 %
97	SEQ ID NO: 70, 137	hsa-miR-1250, hsa-miR-920	85.4 %	85.4 %	85.4 %
98	SEQ ID NO: 252, 62	hsa-miR-497*, hsa-miR-1281	85.3 %	90.6 %	80.0 %
99	SEQ ID NO: 137, 15	hsa-miR-920, hsa-miR-892b	85.3 %	95.0 %	75.6 %
100	SEQ ID NO: 234, 16	hsa-miR-498, hsa-miR-455-3p	85.3 %	90.0 %	80.6 %
101	SEQ ID NO: 24, 269	hsa-miR-330-3p, hsa-miR-105	85.2 %	86.6 %	83.8 %
102	SEQ ID NO: 184, 266	hsa-miR-492, hsa-miR-615-5p	85.2 %	92.6 %	77.8 %
103	SEQ ID NO: 16, 32	hsa-miR-455-3p, hsa-miR-380*	85.1 %	79.4 %	90.8 %
104	SEQ ID NO: 255, 24	hsa-miR-193a-3p, hsa-miR-330-3p	85.1 %	90.2 %	80.0 %
105	SEQ ID NO: 156, 24	hsa-miR-217, hsa-miR-330-3p	84.9 %	89.8 %	80.0 %
106	SEQ ID NO: 24, 22	hsa-miR-330-3p, hsa-miR-20b*	84.9 %	89.6 %	80.2 %
107	SEQ ID NO: 137, 184	hsa-miR-920, hsa-miR-492	84.9 %	95.2 %	74.6 %
108	SEQ ID NO: 243, 95	hsa-miR-151-5p, hsa-miR-135b*	84.8 %	75.2 %	94.4 %
109	SEQ ID NO: 174, 254	hsa-miR-636, hsa-miR-323-3p	84.7 %	75.4 %	94.0 %
110	SEQ ID NO: 254, 255	hsa-miR-323-3p, hsa-miR-193a-3p	84.7 %	85.0 %	84.4 %
111	SEQ ID NO: 71, 35	hsa-miR-30e, hsa-miR-188-3p	84.7 %	89.4 %	80.0 %
112	SEQ ID NO: 22, 32	hsa-miR-20b*, hsa-miR-380*	84.7 %	84.0 %	85.4 %
113	SEQ ID NO: 15, 174	hsa-miR-892b, hsa-miR-636	84.6 %	89.8 %	79.4 %
114	SEQ ID NO: 273, 252	hsa-miR-194*, hsa-miR-497*	84.5 %	99.4 %	69.6 %
115	SEQ ID NO: 242, 244	hsa-let-7i, hsa-miR-874	84.4 %	78.6 %	90.2 %
116	SEQ ID NO: 123, 265	hsa-miR-146b-3p, hsa-miR-129-5p	84.4 %	83.8 %	85.0 %
117	SEQ ID NO: 184, 68	hsa-miR-492, hsa-miR-23b*	84.3 %	89.8 %	78.8 %
118	SEQ ID NO: 35, 242	hsa-miR-188-3p, hsa-let-7i	84.3 %	79.0 %	89.6 %
119	SEQ ID NO: 243, 68	hsa-miR-151-5p, hsa-miR-23b*	84.2 %	84.0 %	84.4 %
120	SEQ ID NO: 19, 32	hsa-miR-767-5p, hsa-miR-380*	84.2 %	79.2 %	89.2 %
121	SEQ ID NO: 22, 232	hsa-miR-20b*, hsa-miR-624	84.1 %	85.0 %	83.2 %
122	SEQ ID NO: 95, 243	hsa-miR-135b*, hsa-miR-151-5p	84.0 %	74.0 %	94.0 %
123	SEQ ID NO: 32, 273	hsa-miR-380*, hsa-miR-194*	83.9 %	87.6 %	80.2 %
124	SEQ ID NO: 68, 32	hsa-miR-23b*, hsa-miR-380*	83.8 %	88.0 %	79.6 %

EP 2 865 765 A1

125	SEQ ID NO: 265, 24	hsa-miR-129-5p, hsa-miR-330-3p	83.7 %	78.4 %	89.0 %
126	SEQ ID NO: 156, 22	hsa-miR-217, hsa-miR-20b*	83.7 %	79.0 %	88.4 %
127	SEQ ID NO: 217, 62	hsa-miR-148b, hsa-miR-1281	83.6 %	84.6 %	82.6 %
128	SEQ ID NO: 15, 156	hsa-miR-892b, hsa-miR-217	83.6 %	88.8 %	78.4 %
129	SEQ ID NO: 123, 174	hsa-miR-146b-3p, hsa-miR-636	83.5 %	92.2 %	74.8 %
130	SEQ ID NO: 68, 70	hsa-miR-23b*, hsa-miR-1250	83.3 %	86.4 %	80.2 %
131	SEQ ID NO: 266, 231	hsa-miR-615-5p, hsa-miR-93	83.3 %	85.0 %	81.6 %
132	SEQ ID NO: 157, 31	hsa-miR-566, hsa-miR-139-5p	83.2 %	94.2 %	72.2 %
133	SEQ ID NO: 70, 32	hsa-miR-1250, hsa-miR-380*	83.0 %	82.0 %	84.0 %
134	SEQ ID NO: 243, 259	hsa-miR-151-5p, hsa-miR-631	83.0 %	81.4 %	84.6 %
135	SEQ ID NO: 31, 16	hsa-miR-139-5p, hsa-miR-455-3p	83.0 %	87.8 %	78.2 %
136	SEQ ID NO: 32, 150	hsa-miR-380*, hsa-miR-1254	82.9 %	80.4 %	85.4 %
137	SEQ ID NO: 71, 255	hsa-miR-30e, hsa-miR-193a-3p	82.9 %	79.4 %	86.4 %
138	SEQ ID NO: 70, 52	hsa-miR-1250, hsa-miR-802	82.9 %	90.4 %	75.4 %
139	SEQ ID NO: 135, 85	hsa-miR-7-1*, hsa-miR-140-5p	82.8 %	81.2 %	84.4 %
140	SEQ ID NO: 252, 137	hsa-miR-497*, hsa-miR-920	82.7 %	93.6 %	71.8 %
141	SEQ ID NO: 135, 255	hsa-miR-7-1*, hsa-miR-193a-3p	82.6 %	80.6 %	84.6 %
142	SEQ ID NO: 70, 252	hsa-miR-1250, hsa-miR-497*	82.6 %	91.8 %	73.4 %
143	SEQ ID NO: 231, 32	hsa-miR-93, hsa-miR-380*	82.5 %	80.0 %	85.0 %
144	SEQ ID NO: 269, 22	hsa-miR-105, hsa-miR-20b*	82.5 %	80.8 %	84.2 %
145	SEQ ID NO: 16, 150	hsa-miR-455-3p, hsa-miR-1254	82.4 %	76.2 %	88.6 %
146	SEQ ID NO: 123, 150	hsa-miR-146b-3p, hsa-miR-1254	82.4 %	89.8 %	75.0 %
147	SEQ ID NO: 259, 157	hsa-miR-631, hsa-miR-566	82.3 %	91.0 %	73.6 %
148	SEQ ID NO: 15, 123	hsa-miR-892b, hsa-miR-146b-3p	82.2 %	94.4 %	70.0 %
149	SEQ ID NO: 31, 32	hsa-miR-139-5p, hsa-miR-380*	82.2 %	83.8 %	80.6 %
150	SEQ ID NO: 259, 231	hsa-miR-631, hsa-miR-93	82.1 %	76.8 %	87.4 %
151	SEQ ID NO: 252, 24	hsa-miR-497*, hsa-miR-330-3p	82.1 %	89.2 %	75.0 %
152	SEQ ID NO: 24, 242	hsa-miR-330-3p, hsa-let-7i	82.0 %	74.0 %	90.0 %
153	SEQ ID NO: 116, 252	hsa-miR-339-3p, hsa-miR-497*	82.0 %	88.6 %	75.4 %
154	SEQ ID NO: 243, 125	hsa-miR-151-5p, hsa-miR-1285	82.0 %	74.8 %	89.2 %
155	SEQ ID NO: 252, 150	hsa-miR-497*, hsa-miR-1254	82.0 %	84.4 %	79.6 %
156	SEQ ID NO: 257, 15	hsa-miR-663b, hsa-miR-892b	82.0 %	88.8 %	75.2 %

EP 2 865 765 A1

			%	%	%
157	SEQ ID NO: 123, 244	hsa-miR-146b-3p, hsa-miR-874	81.9 %	79.2 %	84.6 %
158	SEQ ID NO: 259, 125	hsa-miR-631, hsa-miR-1285	81.9 %	90.2 %	73.6 %
159	SEQ ID NO: 16, 70	hsa-miR-455-3p, hsa-miR-1250	81.7 %	79.8 %	83.6 %
160	SEQ ID NO: 259, 95	hsa-miR-631, hsa-miR-135b*	81.7 %	83.4 %	80.0 %
161	SEQ ID NO: 71, 24	hsa-miR-30e, hsa-miR-330-3p	81.7 %	77.4 %	86.0 %
162	SEQ ID NO: 150, 123	hsa-miR-1254, hsa-miR-146b-3p	81.6 %	88.2 %	75.0 %
163	SEQ ID NO: 22, 269	hsa-miR-20b*, hsa-miR-105	81.5 %	80.2 %	82.8 %
164	SEQ ID NO: 16, 174	hsa-miR-455-3p, hsa-miR-636	81.3 %	75.8 %	86.8 %
165	SEQ ID NO: 95, 156	hsa-miR-135b*, hsa-miR-217	81.2 %	84.2 %	78.2 %
166	SEQ ID NO: 246, 181	hsa-miR-20a, hsa-miR-145	81.0 %	82.0 %	80.0 %
167	SEQ ID NO: 243, 22	hsa-miR-151-5p, hsa-miR-20b*	81.0 %	69.0 %	93.0 %
168	SEQ ID NO: 135, 35	hsa-miR-7-1*, hsa-miR-188-3p	80.9 %	79.0 %	82.8 %
169	SEQ ID NO: 150, 135	hsa-miR-1254, hsa-miR-7-1*	80.8 %	78.8 %	82.8 %
170	SEQ ID NO: 269, 243	hsa-miR-105, hsa-miR-151-5p	80.8 %	85.6 %	76.0 %
171	SEQ ID NO: 66, 169	hsa-miR-1295, hsa-miR-324-3p	80.6 %	82.4 %	78.8 %
172	SEQ ID NO: 150, 15	hsa-miR-1254, hsa-miR-892b	80.6 %	82.8 %	78.4 %
173	SEQ ID NO: 31, 123	hsa-miR-139-5p, hsa-miR-146b-3p	80.3 %	92.2 %	68.4 %
174	SEQ ID NO: 217, 252	hsa-miR-148b, hsa-miR-497*	80.2 %	84.8 %	75.6 %
175	SEQ ID NO: 66, 245	hsa-miR-1295, hsa-miR-106a	80.2 %	81.8 %	78.6 %
176	SEQ ID NO: 266, 257	hsa-miR-615-5p, hsa-miR-663b	80.2 %	76.2 %	84.2 %
177	SEQ ID NO: 269, 232	hsa-miR-105, hsa-miR-624	79.9 %	89.8 %	70.0 %
178	SEQ ID NO: 265, 150	hsa-miR-129-5p, hsa-miR-1254	79.9 %	82.4 %	77.4 %
179	SEQ ID NO: 156, 269	hsa-miR-217, hsa-miR-105	79.9 %	89.8 %	70.0 %
180	SEQ ID NO: 22, 174	hsa-miR-20b*, hsa-miR-636	79.8 %	81.0 %	78.6 %
181	SEQ ID NO: 70, 265	hsa-miR-1250, hsa-miR-129-5p	79.8 %	79.6 %	80.0 %
182	SEQ ID NO: 32, 23	hsa-miR-380*, hsa-miR-491-3p	79.8 %	75.0 %	84.6 %
183	SEQ ID NO: 22, 19	hsa-miR-20b*, hsa-miR-767-5p	79.7 %	88.2 %	71.2 %
184	SEQ ID NO: 253, 71	hsa-miR-345, hsa-miR-30e	79.6 %	79.2 %	80.0 %
185	SEQ ID NO: 244, 125	hsa-miR-874, hsa-miR-1285	79.5 %	84.6 %	74.4 %
186	SEQ ID NO: 70, 259	hsa-miR-1250, hsa-miR-631	79.4 %	79.4 %	79.4 %
187	SEQ ID NO: 174, 135	hsa-miR-636, hsa-miR-7-1*	79.4 %	81.6 %	77.2 %

EP 2 865 765 A1

188	SEQ ID NO: 135, 24	hsa-miR-7-1*, hsa-miR-330-3p	79.4 %	78.2 %	80.6 %
189	SEQ ID NO: 253, 135	hsa-miR-345, hsa-miR-7-1*	79.4 %	88.8 %	70.0 %
190	SEQ ID NO: 32, 259	hsa-miR-380*, hsa-miR-631	79.3 %	76.0 %	82.6 %
191	SEQ ID NO: 123, 22	hsa-miR-146b-3p, hsa-miR-20b*	79.2 %	78.0 %	80.4 %
192	SEQ ID NO: 150, 265	hsa-miR-1254, hsa-miR-129-5p	79.2 %	82.2 %	76.2 %
193	SEQ ID NO: 135, 31	hsa-miR-7-1*, hsa-miR-139-5p	79.2 %	81.6 %	76.8 %
194	SEQ ID NO: 16, 252	hsa-miR-455-3p, hsa-miR-497*	79.1 %	82.6 %	75.6 %
195	SEQ ID NO: 254, 85	hsa-miR-323-3p, hsa-miR-140-5p	78.9 %	63.6 %	94.2 %
196	SEQ ID NO: 174, 71	hsa-miR-636, hsa-miR-30e	78.9 %	80.2 %	77.6 %
197	SEQ ID NO: 242, 259	hsa-let-7i, hsa-miR-631	78.9 %	75.0 %	82.8 %
198	SEQ ID NO: 24, 231	hsa-miR-330-3p, hsa-miR-93	78.9 %	76.4 %	81.4 %
199	SEQ ID NO: 27, 252	hsa-miR-423-5p, hsa-miR-497*	78.8 %	91.8 %	65.8 %
200	SEQ ID NO: 242, 243	hsa-let-7i, hsa-miR-151-5p	78.7 %	87.4 %	70.0 %
201	SEQ ID NO: 22, 244	hsa-miR-20b*, hsa-miR-874	78.6 %	77.0 %	80.2 %
202	SEQ ID NO: 135, 16	hsa-miR-7-1*, hsa-miR-455-3p	78.6 %	73.2 %	84.0 %
203	SEQ ID NO: 95, 253	hsa-miR-135b*, hsa-miR-345	78.5 %	76.8 %	80.2 %
204	SEQ ID NO: 252, 16	hsa-miR-497*, hsa-miR-455-3p	78.5 %	82.0 %	75.0 %
205	SEQ ID NO: 250, 217	hsa-miR-374a, hsa-miR-148b	78.5 %	77.4 %	79.6 %
206	SEQ ID NO: 31, 15	hsa-miR-139-5p, hsa-miR-892b	78.4 %	88.8 %	68.0 %
207	SEQ ID NO: 244, 231	hsa-miR-874, hsa-miR-93	78.4 %	78.4 %	78.4 %
208	SEQ ID NO: 123, 95	hsa-miR-146b-3p, hsa-miR-135b*	78.4 %	82.4 %	74.4 %
209	SEQ ID NO: 71, 85	hsa-miR-30e, hsa-miR-140-5p	78.3 %	75.4 %	81.2 %
210	SEQ ID NO: 255, 35	hsa-miR-193a-3p, hsa-miR-188-3p	78.3 %	91.6 %	65.0 %
211	SEQ ID NO: 156, 266	hsa-miR-217, hsa-miR-615-5p	78.3 %	76.0 %	80.6 %
212	SEQ ID NO: 71, 243	hsa-miR-30e, hsa-miR-151-5p	78.2 %	77.4 %	79.0 %
213	SEQ ID NO: 95, 150	hsa-miR-135b*, hsa-miR-1254	78.2 %	74.0 %	82.4 %
214	SEQ ID NO: 231, 22	hsa-miR-93, hsa-miR-20b*	78.2 %	86.4 %	70.0 %
215	SEQ ID NO: 254, 71	hsa-miR-323-3p, hsa-miR-30e	78.1 %	79.0 %	77.2 %
216	SEQ ID NO: 85, 255	hsa-miR-140-5p, hsa-miR-193a-3p	77.9 %	89.4 %	66.4 %
217	SEQ ID NO: 32, 71	hsa-miR-380*, hsa-miR-30e	77.9 %	74.6 %	81.2 %
218	SEQ ID NO: 174, 255	hsa-miR-636, hsa-miR-193a-3p	77.8 %	79.6 %	76.0 %
219	SEQ ID NO: 232, 135	hsa-miR-624, hsa-miR-7-1*	77.8 %	82.0 %	73.6 %

EP 2 865 765 A1

			%	%	%
220	SEQ ID NO: 85, 35	hsa-miR-140-5p, hsa-miR-188-3p	77.7 %	90.2 %	65.2 %
221	SEQ ID NO: 242, 125	hsa-let-7i, hsa-miR-1285	77.7 %	71.4 %	84.0 %
222	SEQ ID NO: 257, 123	hsa-miR-663b, hsa-miR-146b-3p	77.7 %	84.6 %	70.8 %
223	SEQ ID NO: 265, 15	hsa-miR-129-5p, hsa-miR-892b	77.7 %	80.0 %	75.4 %
224	SEQ ID NO: 32, 232	hsa-miR-380*, hsa-miR-624	77.6 %	81.6 %	73.6 %
225	SEQ ID NO: 41, 251	hsa-miR-654-5p, hsa-miR-182	77.5 %	91.8 %	63.2 %
226	SEQ ID NO: 150, 266	hsa-miR-1254, hsa-miR-615-5p	77.5 %	81.8 %	73.2 %
227	SEQ ID NO: 252, 23	hsa-miR-497*, hsa-miR-491-3p	77.5 %	81.8 %	73.2 %
228	SEQ ID NO: 150, 95	hsa-miR-1254, hsa-miR-135b*	77.4 %	74.4 %	80.4 %
229	SEQ ID NO: 32, 95	hsa-miR-380*, hsa-miR-135b*	77.4 %	79.0 %	75.8 %
230	SEQ ID NO: 155, 247	hsa-miR-484, hsa-miR-148a	77.3 %	81.0 %	73.6 %
231	SEQ ID NO: 22, 31	hsa-miR-20b*, hsa-miR-139-5p	77.3 %	79.8 %	74.8 %
232	SEQ ID NO: 19, 16	hsa-miR-767-5p, hsa-miR-455-3p	77.2 %	75.6 %	78.8 %
233	SEQ ID NO: 244, 135	hsa-miR-874, hsa-miR-7-1*	77.1 %	69.4 %	84.8 %
234	SEQ ID NO: 27, 217	hsa-miR-423-5p, hsa-miR-148b	77.1 %	74.4 %	79.8 %
235	SEQ ID NO: 125, 66	hsa-miR-1285, hsa-miR-1295	77.1 %	79.2 %	75.0 %
236	SEQ ID NO: 125, 155	hsa-miR-1285, hsa-miR-484	77.0 %	67.0 %	87.0 %
237	SEQ ID NO: 16, 137	hsa-miR-455-3p, hsa-miR-920	77.0 %	78.4 %	75.6 %
238	SEQ ID NO: 31, 22	hsa-miR-139-5p, hsa-miR-20b*	76.9 %	79.6 %	74.2 %
239	SEQ ID NO: 116, 16	hsa-miR-339-3p, hsa-miR-455-3p	76.9 %	70.0 %	83.8 %
240	SEQ ID NO: 231, 66	hsa-miR-93, hsa-miR-1295	76.9 %	75.0 %	78.8 %
241	SEQ ID NO: 167, 242	hsa-miR-627, hsa-let-7i	76.5 %	69.2 %	83.8 %
242	SEQ ID NO: 259, 150	hsa-miR-631, hsa-miR-1254	76.3 %	68.6 %	84.0 %
243	SEQ ID NO: 156, 231	hsa-miR-217, hsa-miR-93	76.2 %	80.2 %	72.2 %
244	SEQ ID NO: 59, 181	hsa-miR-1301, hsa-miR-145	76.0 %	86.8 %	65.2 %
245	SEQ ID NO: 71, 242	hsa-miR-30e, hsa-let-7i	76.0 %	72.8 %	79.2 %
246	SEQ ID NO: 125, 231	hsa-miR-1285, hsa-miR-93	75.9 %	73.2 %	78.6 %
247	SEQ ID NO: 24, 244	hsa-miR-330-3p, hsa-miR-874	75.9 %	70.0 %	81.8 %
248	SEQ ID NO: 167, 259	hsa-miR-627, hsa-miR-631	75.8 %	82.2 %	69.4 %
249	SEQ ID NO: 16, 273	hsa-miR-455-3p, hsa-miR-194*	75.8 %	77.4 %	74.2 %
250	SEQ ID NO: 95, 31	hsa-miR-135b*, hsa-miR-139-5p	75.5 %	82.6 %	68.4 %

EP 2 865 765 A1

251	SEQ ID NO: 269, 32	hsa-miR-105, hsa-miR-380*	75.5 %	77.2 %	73.8 %
252	SEQ ID NO: 243, 135	hsa-miR-151-5p, hsa-miR-7-1*	75.5 %	69.8 %	81.2 %
253	SEQ ID NO: 244, 71	hsa-miR-874, hsa-miR-30e	75.4 %	75.0 %	75.8 %
254	SEQ ID NO: 265, 156	hsa-miR-129-5p, hsa-miR-217	75.4 %	85.4 %	65.4 %
255	SEQ ID NO: 231, 269	hsa-miR-93, hsa-miR-105	75.3 %	79.8 %	70.8 %
256	SEQ ID NO: 266, 150	hsa-miR-615-5p, hsa-miR-1254	75.3 %	78.6 %	72.0 %
257	SEQ ID NO: 22, 135	hsa-miR-20b*, hsa-miR-7-1*	75.2 %	70.0 %	80.4 %
258	SEQ ID NO: 244, 66	hsa-miR-874, hsa-miR-1295	75.2 %	80.4 %	70.0 %
259	SEQ ID NO: 150, 156	hsa-miR-1254, hsa-miR-217	74.9 %	71.0 %	78.8 %
260	SEQ ID NO: 156, 243	hsa-miR-217, hsa-miR-151-5p	74.9 %	66.2 %	83.6 %
261	SEQ ID NO: 59, 248	hsa-miR-1301, hsa-let-7b	74.7 %	91.0 %	58.4 %
262	SEQ ID NO: 19, 31	hsa-miR-767-5p, hsa-miR-139-5p	74.7 %	84.6 %	64.8 %
263	SEQ ID NO: 16, 259	hsa-miR-455-3p, hsa-miR-631	74.6 %	66.0 %	83.2 %
264	SEQ ID NO: 24, 167	hsa-miR-330-3p, hsa-miR-627	74.6 %	71.2 %	78.0 %
265	SEQ ID NO: 41, 27	hsa-miR-654-5p, hsa-miR-423-5p	74.5 %	72.4 %	76.6 %
266	SEQ ID NO: 255, 167	hsa-miR-193a-3p, hsa-miR-627	74.4 %	77.8 %	71.0 %
267	SEQ ID NO: 169, 59	hsa-miR-324-3p, hsa-miR-1301	74.3 %	85.4 %	63.2 %
268	SEQ ID NO: 52, 243	hsa-miR-802, hsa-miR-151-5p	73.9 %	76.8 %	71.0 %
269	SEQ ID NO: 174, 244	hsa-miR-636, hsa-miR-874	73.9 %	89.8 %	58.0 %
270	SEQ ID NO: 35, 24	hsa-miR-188-3p, hsa-miR-330-3p	73.9 %	72.6 %	75.2 %
271	SEQ ID NO: 32, 135	hsa-miR-380*, hsa-miR-7-1*	73.9 %	62.0 %	85.8 %
272	SEQ ID NO: 23, 24	hsa-miR-491-3p, hsa-miR-330-3p	73.8 %	69.4 %	78.2 %
273	SEQ ID NO: 169, 246	hsa-miR-324-3p, hsa-miR-20a	73.6 %	72.4 %	74.8 %
274	SEQ ID NO: 125, 245	hsa-miR-1285, hsa-miR-106a	73.4 %	75.0 %	71.8 %
275	SEQ ID NO: 181, 249	hsa-miR-145, hsa-miR-33b*	73.3 %	91.6 %	55.0 %
276	SEQ ID NO: 231, 155	hsa-miR-93, hsa-miR-484	73.2 %	68.4 %	78.0 %
277	SEQ ID NO: 231, 169	hsa-miR-93, hsa-miR-324-3p	73.1 %	66.0 %	80.2 %
278	SEQ ID NO: 273, 24	hsa-miR-194*, hsa-miR-330-3p	72.8 %	79.2 %	66.4 %
279	SEQ ID NO: 248, 41	hsa-let-7b, hsa-miR-654-5p	72.6 %	71.8 %	73.4 %
280	SEQ ID NO: 95, 265	hsa-miR-135b*, hsa-miR-129-5p	72.6 %	72.0 %	73.2 %
281	SEQ ID NO: 59, 12	hsa-miR-1301, hsa-miR-128	72.1 %	89.0 %	55.2 %
282	SEQ ID NO: 244, 245	hsa-miR-874, hsa-miR-106a	72.0 %	68.4 %	75.6 %

EP 2 865 765 A1

			%	%	%
283	SEQ ID NO: 231, 245	hsa-miR-93, hsa-miR-106a	71.9 %	81.4 %	62.4 %
284	SEQ ID NO: 265, 266	hsa-miR-129-5p, hsa-miR-615-5p	71.9 %	78.4 %	65.4 %
285	SEQ ID NO: 266, 22	hsa-miR-615-5p, hsa-miR-20b*	71.9 %	61.2 %	82.6 %
286	SEQ ID NO: 266, 265	hsa-miR-615-5p, hsa-miR-129-5p	71.8 %	78.8 %	64.8 %
287	SEQ ID NO: 70, 150	hsa-miR-1250, hsa-miR-1254	71.6 %	70.4 %	72.8 %
288	SEQ ID NO: 247, 59	hsa-miR-148a, hsa-miR-1301	71.6 %	83.8 %	59.4 %
289	SEQ ID NO: 12, 250	hsa-miR-128, hsa-miR-374a	71.3 %	77.4 %	65.2 %
290	SEQ ID NO: 251, 217	hsa-miR-182, hsa-miR-148b	71.1 %	60.0 %	82.2 %
291	SEQ ID NO: 35, 167	hsa-miR-188-3p, hsa-miR-627	71.0 %	77.0 %	65.0 %
292	SEQ ID NO: 31, 273	hsa-miR-139-5p, hsa-miR-194*	71.0 %	85.2 %	56.8 %
293	SEQ ID NO: 27, 116	hsa-miR-423-5p, hsa-miR-339-3p	70.9 %	69.2 %	72.6 %
294	SEQ ID NO: 135, 254	hsa-miR-7-1*, hsa-miR-323-3p	70.5 %	60.8 %	80.2 %
295	SEQ ID NO: 155, 169	hsa-miR-484, hsa-miR-324-3p	69.9 %	67.4 %	72.4 %
296	SEQ ID NO: 245, 169	hsa-miR-106a, hsa-miR-324-3p	69.9 %	72.0 %	67.8 %
297	SEQ ID NO: 246, 247	hsa-miR-20a, hsa-miR-148a	69.7 %	83.0 %	56.4 %
298	SEQ ID NO: 246, 59	hsa-miR-20a, hsa-miR-1301	69.4 %	80.4 %	58.4 %
299	SEQ ID NO: 248, 249	hsa-let-7b, hsa-miR-33b*	69.3 %	62.4 %	76.2 %
300	SEQ ID NO: 217, 116	hsa-miR-148b, hsa-miR-339-3p	69.0 %	72.0 %	66.0 %
301	SEQ ID NO: 135, 71	hsa-miR-7-1*, hsa-miR-30e	68.5 %	62.8 %	74.2 %
302	SEQ ID NO: 181, 12	hsa-miR-145, hsa-miR-128	68.5 %	72.4 %	64.6 %
303	SEQ ID NO: 259, 244	hsa-miR-631, hsa-miR-874	68.2 %	69.4 %	67.0 %
304	SEQ ID NO: 247, 181	hsa-miR-148a, hsa-miR-145	68.0 %	55.4 %	80.6 %
305	SEQ ID NO: 12, 249	hsa-miR-128, hsa-miR-33b*	67.9 %	56.8 %	79.0 %
306	SEQ ID NO: 273, 23	hsa-miR-194*, hsa-miR-491-3p	67.7 %	75.4 %	60.0 %
307	SEQ ID NO: 169, 247	hsa-miR-324-3p, hsa-miR-148a	67.6 %	69.2 %	66.0 %
308	SEQ ID NO: 248, 12	hsa-let-7b, hsa-miR-128	67.4 %	61.6 %	73.2 %
309	SEQ ID NO: 41, 250	hsa-miR-654-5p, hsa-miR-374a	67.3 %	58.8 %	75.8 %
310	SEQ ID NO: 66, 155	hsa-miR-1295, hsa-miR-484	67.1 %	69.2 %	65.0 %
311	SEQ ID NO: 135, 242	hsa-miR-7-1*, hsa-let-7i	65.8 %	70.2 %	61.4 %
312	SEQ ID NO: 249, 251	hsa-miR-33b*, hsa-miR-182	65.3 %	65.0 %	65.6 %
313	SEQ ID NO: 247, 248	hsa-miR-148a, hsa-let-7b	65.2 %	64.0 %	66.4 %

EP 2 865 765 A1

314	SEQ ID NO: 245, 246	hsa-miR-106a, hsa-miR-20a	64.7 %	77.6 %	51.8 %
315	SEQ ID NO: 12, 41	hsa-miR-128, hsa-miR-654-5p	64.4 %	55.0 %	73.8 %
316	SEQ ID NO: 250, 27	hsa-miR-374a, hsa-miR-423-5p	63.4 %	76.2 %	50.6 %
317	SEQ ID NO: 245, 155	hsa-miR-106a, hsa-miR-484	61.3 %	56.8 %	65.8 %
318	SEQ ID NO: 155, 246	hsa-miR-484, hsa-miR-20a	61.0 %	54.2 %	67.8 %
319	SEQ ID NO: 249, 41	hsa-miR-33b*, hsa-miR-654-5p	60.8 %	56.4 %	65.2 %
320	SEQ ID NO: 251, 27	hsa-miR-182, hsa-miR-423-5p	59.7 %	58.2 %	61.2 %
321	SEQ ID NO: 249, 250	hsa-miR-33b*, hsa-miR-374a	59.6 %	62.8 %	56.4 %
322	SEQ ID NO: 181, 248	hsa-miR-145, hsa-let-7b	57.4 %	55.6 %	59.2 %
323	SEQ ID NO: 251, 116	hsa-miR-182, hsa-miR-339-3p	56.8 %	50.4 %	63.2 %
324	SEQ ID NO: 250, 251	hsa-miR-374a, hsa-miR-182	56.3 %	67.2 %	45.4 %
325	SEQ ID NO: 150, 253, 174	hsa-miR-1254, hsa-miR-345, hsa-miR-636	99.8 %	100.0 %	99.6 %
326	SEQ ID NO: 137, 15, 243	hsa-miR-920, hsa-miR-892b, hsa-miR-151-5p	99.0 %	99.8 %	98.2 %
327	SEQ ID NO: 16, 253, 174	hsa-miR-455-3p, hsa-miR-345, hsa-miR-636	98.1 %	99.2 %	97.0 %
328	SEQ ID NO: 162, 16, 150	hsa-miR-142-5p, hsa-miR-455-3p, hsa-miR-1254	97.5 %	100.0 %	95.0 %
329	SEQ ID NO: 150, 174, 135	hsa-miR-1254, hsa-miR-636, hsa-miR-7-1*	96.5 %	95.6 %	97.4 %
330	SEQ ID NO: 253, 174, 71	hsa-miR-345, hsa-miR-636, hsa-miR-30e	96.3 %	97.0 %	95.6 %
331	SEQ ID NO: 123, 269, 243	hsa-miR-146b-3p, hsa-miR-105, hsa-miR-151-5p	96.2 %	93.8 %	98.6 %
332	SEQ ID NO: 62, 253, 174	hsa-miR-1281, hsa-miR-345, hsa-miR-636	95.8 %	98.0 %	93.6 %
333	SEQ ID NO: 162, 70, 266	hsa-miR-142-5p, hsa-miR-1250, hsa-miR-615-5p	95.5 %	98.8 %	92.2 %
334	SEQ ID NO: 15, 243, 62	hsa-miR-892b, hsa-miR-151-5p, hsa-miR-1281	95.1 %	99.6 %	90.6 %
335	SEQ ID NO: 24, 242, 243	hsa-miR-330-3p, hsa-let-7i, hsa-miR-151-5p	95.0 %	95.0 %	95.0 %
336	SEQ ID NO: 242, 243, 244	hsa-let-7i, hsa-miR-151-5p, hsa-miR-874	95.0 %	95.0 %	95.0 %
337	SEQ ID NO: 71, 243, 244	hsa-miR-30e, hsa-miR-151-5p, hsa-miR-874	95.0 %	90.0 %	100.0 %
338	SEQ ID NO: 243, 16, 32	hsa-miR-151-5p, hsa-miR-455-3p, hsa-miR-380*	94.9 %	94.8 %	95.0 %
339	SEQ ID NO: 243, 244, 125	hsa-miR-151-5p, hsa-miR-874, hsa-miR-1285	94.9 %	90.0 %	99.8 %
340	SEQ ID NO: 252, 137, 243	hsa-miR-497*, hsa-miR-920, hsa-miR-151-5p	94.9 %	89.8 %	100.0 %
341	SEQ ID NO: 174, 254, 71	hsa-miR-636, hsa-miR-323-3p, hsa-miR-30e	94.8 %	99.6 %	90.0 %
342	SEQ ID NO: 52, 137, 162	hsa-miR-802, hsa-miR-920, hsa-miR-142-5p	94.8 %	95.0 %	94.6 %
343	SEQ ID NO: 71, 24, 243	hsa-miR-30e, hsa-miR-330-3p, hsa-miR-151-5p	94.7 %	94.4 %	95.0 %
344	SEQ ID NO: 150, 174, 71	hsa-miR-1254, hsa-miR-636, hsa-miR-30e	94.7 %	89.4 %	100.0 %
345	SEQ ID NO: 35, 24, 243	hsa-miR-188-3p, hsa-miR-330-3p, hsa-	94.6 %	94.8 %	94.4 %

EP 2 865 765 A1

		miR-151-5p	%	%	%
346	SEQ ID NO: 231, 22, 232	hsa-miR-93, hsa-miR-20b*, hsa-miR-624	94.6 %	94.2 %	95.0 %
347	SEQ ID NO: 157, 184, 70	hsa-miR-566, hsa-miR-492, hsa-miR-1250	94.6 %	100.0 %	89.2 %
348	SEQ ID NO: 184, 243, 16	hsa-miR-492, hsa-miR-151-5p, hsa-miR-455-3p	94.5 %	100.0 %	89.0 %
349	SEQ ID NO: 184, 52, 243	hsa-miR-492, hsa-miR-802, hsa-miR-151-5p	94.4 %	96.4 %	92.4 %
350	SEQ ID NO: 243, 244, 231	hsa-miR-151-5p, hsa-miR-874, hsa-miR-93	94.4 %	90.0 %	98.8 %
351	SEQ ID NO: 167, 243, 244	hsa-miR-627, hsa-miR-151-5p, hsa-miR-874	94.2 %	88.4 %	100.0 %
352	SEQ ID NO: 234, 52, 137	hsa-miR-498, hsa-miR-802, hsa-miR-920	94.2 %	95.0 %	93.4 %
353	SEQ ID NO: 254, 71, 255	hsa-miR-323-3p, hsa-miR-30e, hsa-miR-193a-3p	94.1 %	95.4 %	92.8 %
354	SEQ ID NO: 35, 242, 243	hsa-miR-188-3p, hsa-let-7i, hsa-miR-151-5p	94.1 %	94.6 %	93.6 %
355	SEQ ID NO: 137, 52, 243	hsa-miR-920, hsa-miR-802, hsa-miR-151-5p	94.0 %	93.2 %	94.8 %
356	SEQ ID NO: 254, 71, 85	hsa-miR-323-3p, hsa-miR-30e, hsa-miR-140-5p	93.9 %	94.4 %	93.4 %
357	SEQ ID NO: 243, 16, 70	hsa-miR-151-5p, hsa-miR-455-3p, hsa-miR-1250	93.9 %	90.4 %	97.4 %
358	SEQ ID NO: 15, 243, 95	hsa-miR-892b, hsa-miR-151-5p, hsa-miR-135b*	93.9 %	97.4 %	90.4 %
359	SEQ ID NO: 137, 162, 70	hsa-miR-920, hsa-miR-142-5p, hsa-miR-1250	93.9 %	95.0 %	92.8 %
360	SEQ ID NO: 52, 157, 184	hsa-miR-802, hsa-miR-566, hsa-miR-492	93.3 %	99.8 %	86.8 %
361	SEQ ID NO: 162, 252, 16	hsa-miR-142-5p, hsa-miR-497*, hsa-miR-455-3p	93.2 %	91.6 %	94.8 %
362	SEQ ID NO: 15, 123, 269	hsa-miR-892b, hsa-miR-146b-3p, hsa-miR-105	92.9 %	95.8 %	90.0 %
363	SEQ ID NO: 174, 244, 254	hsa-miR-636, hsa-miR-874, hsa-miR-323-3p	92.8 %	88.2 %	97.4 %
364	SEQ ID NO: 167, 242, 243	hsa-miR-627, hsa-let-7i, hsa-miR-151-5p	92.8 %	94.8 %	90.8 %
365	SEQ ID NO: 243, 123, 150	hsa-miR-151-5p, hsa-miR-146b-3p, hsa-miR-1254	92.8 %	86.2 %	99.4 %
366	SEQ ID NO: 252, 184, 243	hsa-miR-497*, hsa-miR-492, hsa-miR-151-5p	92.7 %	99.6 %	85.8 %
367	SEQ ID NO: 162, 234, 68	hsa-miR-142-5p, hsa-miR-498, hsa-miR-23b*	92.7 %	90.4 %	95.0 %
368	SEQ ID NO: 234, 68, 70	hsa-miR-498, hsa-miR-23b*, hsa-miR-1250	92.7 %	95.4 %	90.0 %
369	SEQ ID NO: 135, 24, 243	hsa-miR-7-1*, hsa-miR-330-3p, hsa-miR-151-5p	92.6 %	95.0 %	90.2 %
370	SEQ ID NO: 24, 167, 243	hsa-miR-330-3p, hsa-miR-627, hsa-miR-151-5p	92.6 %	95.0 %	90.2 %
371	SEQ ID NO: 234, 62, 52	hsa-miR-498, hsa-miR-1281, hsa-miR-802	92.5 %	95.0 %	90.0 %
372	SEQ ID NO: 162, 135, 24	hsa-miR-142-5p, hsa-miR-7-1*, hsa-miR-330-3p	92.5 %	95.0 %	90.0 %
373	SEQ ID NO: 24, 243, 244	hsa-miR-330-3p, hsa-miR-151-5p, hsa-miR-874	92.5 %	90.0 %	95.0 %
374	SEQ ID NO: 162, 62, 150	hsa-miR-142-5p, hsa-miR-1281, hsa-miR-1254	92.5 %	95.0 %	90.0 %
375	SEQ ID NO: 15, 62, 95	hsa-miR-892b, hsa-miR-1281, hsa-miR-135b*	92.5 %	100.0 %	85.0 %
376	SEQ ID NO: 234, 68, 52	hsa-miR-498, hsa-miR-23b*, hsa-miR-802	92.5 %	95.0 %	90.0 %

EP 2 865 765 A1

377	SEQ ID NO: 234, 68, 137	hsa-miR-498, hsa-miR-23b*, hsa-miR-920	92.5 %	94.0 %	91.0 %
378	SEQ ID NO: 68, 52, 184	hsa-miR-23b*, hsa-miR-802, hsa-miR-492	92.5 %	95.0 %	90.0 %
379	SEQ ID NO: 162, 234, 252	hsa-miR-142-5p, hsa-miR-498, hsa-miR-497*	92.4 %	89.8 %	95.0 %
380	SEQ ID NO: 184, 52, 68	hsa-miR-492, hsa-miR-802, hsa-miR-23b*	92.4 %	94.8 %	90.0 %
381	SEQ ID NO: 184, 52, 16	hsa-miR-492, hsa-miR-802, hsa-miR-455-3p	92.4 %	99.8 %	85.0 %
382	SEQ ID NO: 243, 244, 245	hsa-miR-151-5p, hsa-miR-874, hsa-miR-106a	92.4 %	89.4 %	95.4 %
383	SEQ ID NO: 62, 16, 253	hsa-miR-1281, hsa-miR-455-3p, hsa-miR-345	92.4 %	95.0 %	89.8 %
384	SEQ ID NO: 22, 269, 232	hsa-miR-20b*, hsa-miR-105, hsa-miR-624	92.4 %	99.2 %	85.6 %
385	SEQ ID NO: 266, 24, 269	hsa-miR-615-5p, hsa-miR-330-3p, hsa-miR-105	92.4 %	99.8 %	85.0 %
386	SEQ ID NO: 15, 95, 269	hsa-miR-892b, hsa-miR-135b*, hsa-miR-105	92.4 %	99.8 %	85.0 %
387	SEQ ID NO: 157, 137, 70	hsa-miR-566, hsa-miR-920, hsa-miR-1250	92.4 %	95.2 %	89.6 %
388	SEQ ID NO: 162, 265, 150	hsa-miR-142-5p, hsa-miR-129-5p, hsa-miR-1254	92.4 %	90.2 %	94.6 %
389	SEQ ID NO: 243, 68, 16	hsa-miR-151-5p, hsa-miR-23b*, hsa-miR-455-3p	92.3 %	95.6 %	89.0 %
390	SEQ ID NO: 15, 62, 123	hsa-miR-892b, hsa-miR-1281, hsa-miR-146b-3p	92.3 %	99.6 %	85.0 %
391	SEQ ID NO: 137, 52, 62	hsa-miR-920, hsa-miR-802, hsa-miR-1281	92.3 %	100.0 %	84.6 %
392	SEQ ID NO: 62, 150, 253	hsa-miR-1281, hsa-miR-1254, hsa-miR-345	92.2 %	95.0 %	89.4 %
393	SEQ ID NO: 52, 62, 123	hsa-miR-802, hsa-miR-1281, hsa-miR-146b-3p	92.2 %	99.4 %	85.0 %
394	SEQ ID NO: 52, 137, 184	hsa-miR-802, hsa-miR-920, hsa-miR-492	92.2 %	95.2 %	89.2 %
395	SEQ ID NO: 253, 31, 123	hsa-miR-345, hsa-miR-139-5p, hsa-miR-146b-3p	92.1 %	94.2 %	90.0 %
396	SEQ ID NO: 162, 71, 24	hsa-miR-142-5p, hsa-miR-30e, hsa-miR-330-3p	92.1 %	91.2 %	93.0 %
397	SEQ ID NO: 16, 150, 174	hsa-miR-455-3p, hsa-miR-1254, hsa-miR-636	92.1 %	85.4 %	98.8 %
398	SEQ ID NO: 62, 123, 95	hsa-miR-1281, hsa-miR-146b-3p, hsa-miR-135b*	92.1 %	99.2 %	85.0 %
399	SEQ ID NO: 62, 150, 265	hsa-miR-1281, hsa-miR-1254, hsa-miR-129-5p	92.1 %	94.6 %	89.6 %
400	SEQ ID NO: 52, 184, 162	hsa-miR-802, hsa-miR-492, hsa-miR-142-5p	92.1 %	94.6 %	89.6 %
401	SEQ ID NO: 24, 243, 125	hsa-miR-330-3p, hsa-miR-151-5p, hsa-miR-1285	92.0 %	93.4 %	90.6 %
402	SEQ ID NO: 68, 16, 137	hsa-miR-23b*, hsa-miR-455-3p, hsa-miR-920	92.0 %	99.0 %	85.0 %
403	SEQ ID NO: 68, 252, 137	hsa-miR-23b*, hsa-miR-497*, hsa-miR-920	92.0 %	99.6 %	84.4 %
404	SEQ ID NO: 234, 184, 16	hsa-miR-498, hsa-miR-492, hsa-miR-455-3p	91.9 %	93.2 %	90.6 %
405	SEQ ID NO: 62, 123, 150	hsa-miR-1281, hsa-miR-146b-3p, hsa-miR-1254	91.9 %	98.8 %	85.0 %
406	SEQ ID NO: 234, 68, 16	hsa-miR-498, hsa-miR-23b*, hsa-miR-455-3p	91.9 %	93.8 %	90.0 %
407	SEQ ID NO: 62, 184, 52	hsa-miR-1281, hsa-miR-492, hsa-miR-802	91.8 %	95.0 %	88.6 %
408	SEQ ID NO: 162, 252, 62	hsa-miR-142-5p, hsa-miR-497*, hsa-miR-	91.8 %	95.2 %	88.4 %

EP 2 865 765 A1

		1281	%	%	%
409	SEQ ID NO: 253, 15, 123	hsa-miR-345, hsa-miR-892b, hsa-miR-146b-3p	91.8 %	94.6 %	89.0 %
410	SEQ ID NO: 243, 259, 231	hsa-miR-151-5p, hsa-miR-631, hsa-miR-93	91.8 %	89.8 %	93.8 %
411	SEQ ID NO: 265, 150, 257	hsa-miR-129-5p, hsa-miR-1254, hsa-miR-663b	91.8 %	93.8 %	89.8 %
412	SEQ ID NO: 157, 184, 68	hsa-miR-566, hsa-miR-492, hsa-miR-23b*	91.6 %	98.6 %	84.6 %
413	SEQ ID NO: 243, 135, 19	hsa-miR-151-5p, hsa-miR-7-1*, hsa-miR-767-5p	91.6 %	88.8 %	94.4 %
414	SEQ ID NO: 68, 157, 184	hsa-miR-23b*, hsa-miR-566, hsa-miR-492	91.6 %	98.4 %	84.8 %
415	SEQ ID NO: 234, 252, 52	hsa-miR-498, hsa-miR-497*, hsa-miR-802	91.5 %	93.2 %	89.8 %
416	SEQ ID NO: 52, 15, 62	hsa-miR-802, hsa-miR-892b, hsa-miR-1281	91.5 %	100.0 %	83.0 %
417	SEQ ID NO: 68, 52, 137	hsa-miR-23b*, hsa-miR-802, hsa-miR-920	91.5 %	98.6 %	84.4 %
418	SEQ ID NO: 157, 162, 70	hsa-miR-566, hsa-miR-142-5p, hsa-miR-1250	91.5 %	95.4 %	87.6 %
419	SEQ ID NO: 157, 234, 184	hsa-miR-566, hsa-miR-498, hsa-miR-492	91.4 %	93.2 %	89.6 %
420	SEQ ID NO: 252, 184, 52	hsa-miR-497*, hsa-miR-492, hsa-miR-802	91.3 %	98.8 %	83.8 %
421	SEQ ID NO: 162, 62, 16	hsa-miR-142-5p, hsa-miR-1281, hsa-miR-455-3p	91.3 %	95.6 %	87.0 %
422	SEQ ID NO: 137, 15, 62	hsa-miR-920, hsa-miR-892b, hsa-miR-1281	91.3 %	99.6 %	83.0 %
423	SEQ ID NO: 137, 243, 62	hsa-miR-920, hsa-miR-151-5p, hsa-miR-1281	91.3 %	95.4 %	87.2 %
424	SEQ ID NO: 217, 62, 16	hsa-miR-148b, hsa-miR-1281, hsa-miR-455-3p	91.2 %	97.4 %	85.0 %
425	SEQ ID NO: 259, 150, 157	hsa-miR-631, hsa-miR-1254, hsa-miR-566	91.1 %	97.4 %	84.8 %
426	SEQ ID NO: 24, 243, 259	hsa-miR-330-3p, hsa-miR-151-5p, hsa-miR-631	91.1 %	90.0 %	92.2 %
427	SEQ ID NO: 234, 252, 184	hsa-miR-498, hsa-miR-497*, hsa-miR-492	91.0 %	89.2 %	92.8 %
428	SEQ ID NO: 95, 253, 15	hsa-miR-135b*, hsa-miR-345, hsa-miR-892b	91.0 %	94.2 %	87.8 %
429	SEQ ID NO: 157, 68, 16	hsa-miR-566, hsa-miR-23b*, hsa-miR-455-3p	91.0 %	99.2 %	82.8 %
430	SEQ ID NO: 266, 265, 257	hsa-miR-615-5p, hsa-miR-129-5p, hsa-miR-663b	91.0 %	94.2 %	87.8 %
431	SEQ ID NO: 269, 135, 19	hsa-miR-105, hsa-miR-7-1*, hsa-miR-767-5p	91.0 %	89.6 %	92.4 %
432	SEQ ID NO: 257, 157, 184	hsa-miR-663b, hsa-miR-566, hsa-miR-492	90.9 %	98.6 %	83.2 %
433	SEQ ID NO: 243, 62, 150	hsa-miR-151-5p, hsa-miR-1281, hsa-miR-1254	90.7 %	95.2 %	86.2 %
434	SEQ ID NO: 184, 162, 266	hsa-miR-492, hsa-miR-142-5p, hsa-miR-615-5p	90.7 %	93.0 %	88.4 %
435	SEQ ID NO: 244, 254, 71	hsa-miR-874, hsa-miR-323-3p, hsa-miR-30e	90.6 %	85.2 %	96.0 %
436	SEQ ID NO: 62, 52, 68	hsa-miR-1281, hsa-miR-802, hsa-miR-23b*	90.6 %	96.8 %	84.4 %
437	SEQ ID NO: 162, 252, 150	hsa-miR-142-5p, hsa-miR-497*, hsa-miR-1254	90.6 %	91.0 %	90.2 %
438	SEQ ID NO: 243, 62, 123	hsa-miR-151-5p, hsa-miR-1281, hsa-miR-146b-3p	90.6 %	94.6 %	86.6 %
439	SEQ ID NO: 68, 16, 252	hsa-miR-23b*, hsa-miR-455-3p, hsa-miR-497*	90.6 %	96.2 %	85.0 %

EP 2 865 765 A1

440	SEQ ID NO: 184, 68, 252	hsa-miR-492, hsa-miR-23b*, hsa-miR-497*	90.6 %	96.4 %	84.8 %
441	SEQ ID NO: 16, 137, 52	hsa-miR-455-3p, hsa-miR-920, hsa-miR-802	90.6 %	97.4 %	83.8 %
442	SEQ ID NO: 234, 184, 52	hsa-miR-498, hsa-miR-492, hsa-miR-802	90.5 %	91.0 %	90.0 %
443	SEQ ID NO: 243, 70, 32	hsa-miR-151-5p, hsa-miR-1250, hsa-miR-380*	90.5 %	86.0 %	95.0 %
444	SEQ ID NO: 243, 259, 244	hsa-miR-151-5p, hsa-miR-631, hsa-miR-874	90.5 %	85.0 %	96.0 %
445	SEQ ID NO: 234, 184, 70	hsa-miR-498, hsa-miR-492, hsa-miR-1250	90.5 %	91.0 %	90.0 %
446	SEQ ID NO: 123, 156, 243	hsa-miR-146b-3p, hsa-miR-217, hsa-miR-151-5p	90.5 %	89.6 %	91.4 %
447	SEQ ID NO: 243, 19, 31	hsa-miR-151-5p, hsa-miR-767-5p, hsa-miR-139-5p	90.5 %	92.0 %	89.0 %
448	SEQ ID NO: 234, 252, 62	hsa-miR-498, hsa-miR-497*, hsa-miR-1281	90.3 %	90.6 %	90.0 %
449	SEQ ID NO: 162, 157, 184	hsa-miR-142-5p, hsa-miR-566, hsa-miR-492	90.3 %	95.6 %	85.0 %
450	SEQ ID NO: 162, 157, 68	hsa-miR-142-5p, hsa-miR-566, hsa-miR-23b*	90.3 %	90.6 %	90.0 %
451	SEQ ID NO: 157, 234, 16	hsa-miR-566, hsa-miR-498, hsa-miR-455-3p	90.3 %	95.8 %	84.8 %
452	SEQ ID NO: 234, 52, 157	hsa-miR-498, hsa-miR-802, hsa-miR-566	90.3 %	90.8 %	89.8 %
453	SEQ ID NO: 162, 234, 62	hsa-miR-142-5p, hsa-miR-498, hsa-miR-1281	90.2 %	90.2 %	90.2 %
454	SEQ ID NO: 52, 243, 16	hsa-miR-802, hsa-miR-151-5p, hsa-miR-455-3p	90.2 %	91.0 %	89.4 %
455	SEQ ID NO: 62, 52, 243	hsa-miR-1281, hsa-miR-802, hsa-miR-151-5p	90.2 %	92.4 %	88.0 %
456	SEQ ID NO: 162, 135, 242	hsa-miR-142-5p, hsa-miR-7-1*, hsa-let-7i	90.2 %	93.8 %	86.6 %
457	SEQ ID NO: 68, 70, 137	hsa-miR-23b*, hsa-miR-1250, hsa-miR-920	90.2 %	94.8 %	85.6 %
458	SEQ ID NO: 157, 137, 162	hsa-miR-566, hsa-miR-920, hsa-miR-142-5p	90.2 %	90.0 %	90.4 %
459	SEQ ID NO: 157, 184, 162	hsa-miR-566, hsa-miR-492, hsa-miR-142-5p	90.2 %	95.4 %	85.0 %
460	SEQ ID NO: 123, 22, 174	hsa-miR-146b-3p, hsa-miR-20b*, hsa-miR-636	90.1 %	91.4 %	88.8 %
461	SEQ ID NO: 266, 150, 257	hsa-miR-615-5p, hsa-miR-1254, hsa-miR-663b	90.1 %	93.4 %	86.8 %
462	SEQ ID NO: 123, 156, 269	hsa-miR-146b-3p, hsa-miR-217, hsa-miR-105	90.1 %	99.0 %	81.2 %
463	SEQ ID NO: 22, 135, 16	hsa-miR-20b*, hsa-miR-7-1*, hsa-miR-455-3p	90.1 %	90.0 %	90.2 %
464	SEQ ID NO: 68, 16, 259	hsa-miR-23b*, hsa-miR-455-3p, hsa-miR-631	90.0 %	96.4 %	83.6 %
465	SEQ ID NO: 243, 125, 231	hsa-miR-151-5p, hsa-miR-1285, hsa-miR-93	90.0 %	87.6 %	92.4 %
466	SEQ ID NO: 62, 150, 174	hsa-miR-1281, hsa-miR-1254, hsa-miR-636	90.0 %	95.0 %	85.0 %
467	SEQ ID NO: 252, 62, 253	hsa-miR-497*, hsa-miR-1281, hsa-miR-345	90.0 %	90.2 %	89.8 %
468	SEQ ID NO: 252, 150, 253	hsa-miR-497*, hsa-miR-1254, hsa-miR-345	90.0 %	95.0 %	85.0 %
469	SEQ ID NO: 68, 157, 137	hsa-miR-23b*, hsa-miR-566, hsa-miR-920	90.0 %	95.0 %	85.0 %
470	SEQ ID NO: 162, 70, 150	hsa-miR-142-5p, hsa-miR-1250, hsa-miR-1254	90.0 %	95.4 %	84.6 %
471	SEQ ID NO: 150, 95, 157	hsa-miR-1254, hsa-miR-135b*, hsa-miR-	89.9 %	100.0 %	79.8 %

EP 2 865 765 A1

		566	%	%	%
472	SEQ ID NO: 62, 184, 243	hsa-miR-1281, hsa-miR-492, hsa-miR-151-5p	89.9 %	94.6 %	85.2 %
473	SEQ ID NO: 15, 22, 174	hsa-miR-892b, hsa-miR-20b*, hsa-miR-636	89.9 %	94.0 %	85.8 %
474	SEQ ID NO: 157, 184, 16	hsa-miR-566, hsa-miR-492, hsa-miR-455-3p	89.9 %	95.0 %	84.8 %
475	SEQ ID NO: 137, 70, 266	hsa-miR-920, hsa-miR-1250, hsa-miR-615-5p	89.9 %	94.8 %	85.0 %
476	SEQ ID NO: 150, 15, 123	hsa-miR-1254, hsa-miR-892b, hsa-miR-146b-3p	89.8 %	99.6 %	80.0 %
477	SEQ ID NO: 22, 174, 254	hsa-miR-20b*, hsa-miR-636, hsa-miR-323-3p	89.7 %	84.8 %	94.6 %
478	SEQ ID NO: 62, 95, 150	hsa-miR-1281, hsa-miR-135b*, hsa-miR-1254	89.7 %	98.4 %	81.0 %
479	SEQ ID NO: 52, 15, 123	hsa-miR-802, hsa-miR-892b, hsa-miR-146b-3p	89.7 %	100.0 %	79.4 %
480	SEQ ID NO: 184, 162, 70	hsa-miR-492, hsa-miR-142-5p, hsa-miR-1250	89.7 %	94.4 %	85.0 %
481	SEQ ID NO: 234, 157, 137	hsa-miR-498, hsa-miR-566, hsa-miR-920	89.7 %	89.4 %	90.0 %
482	SEQ ID NO: 259, 95, 157	hsa-miR-631, hsa-miR-135b*, hsa-miR-566	89.6 %	99.2 %	80.0 %
483	SEQ ID NO: 162, 252, 184	hsa-miR-142-5p, hsa-miR-497*, hsa-miR-492	89.6 %	94.2 %	85.0 %
484	SEQ ID NO: 150, 253, 31	hsa-miR-1254, hsa-miR-345, hsa-miR-139-5p	89.6 %	94.2 %	85.0 %
485	SEQ ID NO: 243, 125, 245	hsa-miR-151-5p, hsa-miR-1285, hsa-miR-106a	89.6 %	85.4 %	93.8 %
486	SEQ ID NO: 41, 27, 217	hsa-miR-654-5p, hsa-miR-423-5p, hsa-miR-148b	89.6 %	89.4 %	89.8 %
487	SEQ ID NO: 252, 16, 253	hsa-miR-497*, hsa-miR-455-3p, hsa-miR-345	89.6 %	89.4 %	89.8 %
488	SEQ ID NO: 157, 234, 68	hsa-miR-566, hsa-miR-498, hsa-miR-23b*	89.6 %	89.0 %	90.2 %
489	SEQ ID NO: 62, 95, 265	hsa-miR-1281, hsa-miR-135b*, hsa-miR-129-5p	89.6 %	94.8 %	84.4 %
490	SEQ ID NO: 234, 62, 184	hsa-miR-498, hsa-miR-1281, hsa-miR-492	89.5 %	89.0 %	90.0 %
491	SEQ ID NO: 252, 62, 243	hsa-miR-497*, hsa-miR-1281, hsa-miR-151-5p	89.5 %	94.4 %	84.6 %
492	SEQ ID NO: 253, 123, 22	hsa-miR-345, hsa-miR-146b-3p, hsa-miR-20b*	89.5 %	88.6 %	90.4 %
493	SEQ ID NO: 52, 243, 62	hsa-miR-802, hsa-miR-151-5p, hsa-miR-1281	89.5 %	91.6 %	87.4 %
494	SEQ ID NO: 257, 234, 184	hsa-miR-663b, hsa-miR-498, hsa-miR-492	89.5 %	84.8 %	94.2 %
495	SEQ ID NO: 234, 68, 157	hsa-miR-498, hsa-miR-23b*, hsa-miR-566	89.5 %	89.0 %	90.0 %
496	SEQ ID NO: 15, 156, 269	hsa-miR-892b, hsa-miR-217, hsa-miR-105	89.5 %	89.8 %	89.2 %
497	SEQ ID NO: 253, 15, 22	hsa-miR-345, hsa-miR-892b, hsa-miR-20b*	89.4 %	90.0 %	88.8 %
498	SEQ ID NO: 162, 24, 242	hsa-miR-142-5p, hsa-miR-330-3p, hsa-let-7i	89.4 %	85.8 %	93.0 %
499	SEQ ID NO: 62, 16, 174	hsa-miR-1281, hsa-miR-455-3p, hsa-miR-636	89.4 %	94.4 %	84.4 %
500	SEQ ID NO: 184, 68, 70	hsa-miR-492, hsa-miR-23b*, hsa-miR-1250	89.4 %	89.4 %	89.4 %
501	SEQ ID NO: 137, 162, 266	hsa-miR-920, hsa-miR-142-5p, hsa-miR-615-5p	89.4 %	88.6 %	90.2 %
502	SEQ ID NO: 68, 137, 184	hsa-miR-23b*, hsa-miR-920, hsa-miR-492	89.4 %	94.4 %	84.4 %

EP 2 865 765 A1

503	SEQ ID NO: 253, 31, 15	hsa-miR-345, hsa-miR-139-5p, hsa-miR-892b	89.3 %	89.6 %	89.0 %
504	SEQ ID NO: 52, 15, 243	hsa-miR-802, hsa-miR-892b, hsa-miR-151-5p	89.3 %	95.4 %	83.2 %
505	SEQ ID NO: 22, 269, 135	hsa-miR-20b*, hsa-miR-105, hsa-miR-7-1*	89.3 %	89.6 %	89.0 %
506	SEQ ID NO: 68, 52, 157	hsa-miR-23b*, hsa-miR-802, hsa-miR-566	89.3 %	98.4 %	80.2 %
507	SEQ ID NO: 41, 250, 217	hsa-miR-654-5p, hsa-miR-374a, hsa-miR-148b	89.2 %	86.2 %	92.2 %
508	SEQ ID NO: 184, 70, 252	hsa-miR-492, hsa-miR-1250, hsa-miR-497*	89.2 %	94.8 %	83.6 %
509	SEQ ID NO: 137, 184, 162	hsa-miR-920, hsa-miR-492, hsa-miR-142-5p	89.2 %	90.4 %	88.0 %
510	SEQ ID NO: 123, 95, 269	hsa-miR-146b-3p, hsa-miR-135b*, hsa-miR-105	89.2 %	93.8 %	84.6 %
511	SEQ ID NO: 269, 22, 135	hsa-miR-105, hsa-miR-20b*, hsa-miR-7-1*	89.2 %	89.0 %	89.4 %
512	SEQ ID NO: 15, 123, 156	hsa-miR-892b, hsa-miR-146b-3p, hsa-miR-217	89.1 %	99.4 %	78.8 %
513	SEQ ID NO: 243, 68, 70	hsa-miR-151-5p, hsa-miR-23b*, hsa-miR-1250	89.0 %	88.8 %	89.2 %
514	SEQ ID NO: 52, 68, 16	hsa-miR-802, hsa-miR-23b*, hsa-miR-455-3p	89.0 %	99.2 %	78.8 %
515	SEQ ID NO: 62, 16, 150	hsa-miR-1281, hsa-miR-455-3p, hsa-miR-1254	89.0 %	98.0 %	80.0 %
516	SEQ ID NO: 32, 273, 252	hsa-miR-380*, hsa-miR-194*, hsa-miR-497*	89.0 %	89.8 %	88.2 %
517	SEQ ID NO: 253, 174, 135	hsa-miR-345, hsa-miR-636, hsa-miR-7-1*	88.9 %	93.4 %	84.4 %
518	SEQ ID NO: 259, 125, 231	hsa-miR-631, hsa-miR-1285, hsa-miR-93	88.9 %	89.8 %	88.0 %
519	SEQ ID NO: 231, 22, 269	hsa-miR-93, hsa-miR-20b*, hsa-miR-105	88.9 %	93.0 %	84.8 %
520	SEQ ID NO: 265, 266, 24	hsa-miR-129-5p, hsa-miR-615-5p, hsa-miR-330-3p	88.9 %	93.8 %	84.0 %
521	SEQ ID NO: 70, 252, 15	hsa-miR-1250, hsa-miR-497*, hsa-miR-892b	88.9 %	99.8 %	78.0 %
522	SEQ ID NO: 174, 71, 35	hsa-miR-636, hsa-miR-30e, hsa-miR-188-3p	88.8 %	90.0 %	87.6 %
523	SEQ ID NO: 243, 123, 95	hsa-miR-151-5p, hsa-miR-146b-3p, hsa-miR-135b*	88.8 %	82.8 %	94.8 %
524	SEQ ID NO: 123, 95, 243	hsa-miR-146b-3p, hsa-miR-135b*, hsa-miR-151-5p	88.8 %	83.8 %	93.8 %
525	SEQ ID NO: 157, 253, 123	hsa-miR-566, hsa-miR-345, hsa-miR-146b-3p	88.7 %	91.8 %	85.6 %
526	SEQ ID NO: 135, 35, 24	hsa-miR-7-1*, hsa-miR-188-3p, hsa-miR-330-3p	88.7 %	86.2 %	91.2 %
527	SEQ ID NO: 32, 232, 71	hsa-miR-380*, hsa-miR-624, hsa-miR-30e	88.7 %	93.2 %	84.2 %
528	SEQ ID NO: 162, 184, 68	hsa-miR-142-5p, hsa-miR-492, hsa-miR-23b*	88.7 %	90.0 %	87.4 %
529	SEQ ID NO: 157, 137, 184	hsa-miR-566, hsa-miR-920, hsa-miR-492	88.7 %	98.4 %	79.0 %
530	SEQ ID NO: 162, 70, 265	hsa-miR-142-5p, hsa-miR-1250, hsa-miR-129-5p	88.7 %	85.4 %	92.0 %
531	SEQ ID NO: 95, 269, 22	hsa-miR-135b*, hsa-miR-105, hsa-miR-20b*	88.7 %	92.4 %	85.0 %
532	SEQ ID NO: 252, 15, 243	hsa-miR-497*, hsa-miR-892b, hsa-miR-151-5p	88.6 %	99.8 %	77.4 %
533	SEQ ID NO: 22, 19, 16	hsa-miR-20b*, hsa-miR-767-5p, hsa-miR-455-3p	88.6 %	87.2 %	90.0 %
534	SEQ ID NO: 243, 231,	hsa-miR-151-5p, hsa-miR-93, hsa-miR-	88.5	88.6	88.4

EP 2 865 765 A1

	245	106a	%	%	%
535	SEQ ID NO: 68, 70, 252	hsa-miR-23b*, hsa-miR-1250, hsa-miR-497*	88.5 %	94.8 %	82.2 %
536	SEQ ID NO: 123, 265, 156	hsa-miR-146b-3p, hsa-miR-129-5p, hsa-miR-217	88.5 %	92.2 %	84.8 %
537	SEQ ID NO: 70, 266, 150	hsa-miR-1250, hsa-miR-615-5p, hsa-miR-1254	88.4 %	99.8 %	77.0 %
538	SEQ ID NO: 150, 257, 123	hsa-miR-1254, hsa-miR-663b, hsa-miR-146b-3p	88.4 %	95.0 %	81.8 %
539	SEQ ID NO: 52, 16, 70	hsa-miR-802, hsa-miR-455-3p, hsa-miR-1250	88.3 %	96.6 %	80.0 %
540	SEQ ID NO: 150, 257, 95	hsa-miR-1254, hsa-miR-663b, hsa-miR-135b*	88.3 %	95.4 %	81.2 %
541	SEQ ID NO: 22, 244, 254	hsa-miR-20b*, hsa-miR-874, hsa-miR-323-3p	88.2 %	86.4 %	90.0 %
542	SEQ ID NO: 135, 85, 255	hsa-miR-7-1*, hsa-miR-140-5p, hsa-miR-193a-3p	88.2 %	85.0 %	91.4 %
543	SEQ ID NO: 116, 62, 16	hsa-miR-339-3p, hsa-miR-1281, hsa-miR-455-3p	88.2 %	94.2 %	82.2 %
544	SEQ ID NO: 257, 162, 157	hsa-miR-663b, hsa-miR-142-5p, hsa-miR-566	88.2 %	89.6 %	86.8 %
545	SEQ ID NO: 257, 162, 184	hsa-miR-663b, hsa-miR-142-5p, hsa-miR-492	88.2 %	92.8 %	83.6 %
546	SEQ ID NO: 62, 123, 265	hsa-miR-1281, hsa-miR-146b-3p, hsa-miR-129-5p	88.2 %	91.4 %	85.0 %
547	SEQ ID NO: 95, 269, 243	hsa-miR-135b*, hsa-miR-105, hsa-miR-151-5p	88.2 %	89.6 %	86.8 %
548	SEQ ID NO: 252, 62, 52	hsa-miR-497*, hsa-miR-1281, hsa-miR-802	88.1 %	95.6 %	80.6 %
549	SEQ ID NO: 162, 62, 184	hsa-miR-142-5p, hsa-miR-1281, hsa-miR-492	88.1 %	90.8 %	85.4 %
550	SEQ ID NO: 252, 62, 150	hsa-miR-497*, hsa-miR-1281, hsa-miR-1254	88.1 %	97.8 %	78.4 %
551	SEQ ID NO: 68, 16, 70	hsa-miR-23b*, hsa-miR-455-3p, hsa-miR-1250	88.0 %	92.0 %	84.0 %
552	SEQ ID NO: 123, 174, 135	hsa-miR-146b-3p, hsa-miR-636, hsa-miR-7-1*	88.0 %	94.4 %	81.6 %
553	SEQ ID NO: 162, 266, 265	hsa-miR-142-5p, hsa-miR-615-5p, hsa-miR-129-5p	88.0 %	87.4 %	88.6 %
554	SEQ ID NO: 135, 31, 16	hsa-miR-7-1*, hsa-miR-139-5p, hsa-miR-455-3p	88.0 %	85.6 %	90.4 %
555	SEQ ID NO: 95, 157, 31	hsa-miR-135b*, hsa-miR-566, hsa-miR-139-5p	87.9 %	100.0 %	75.8 %
556	SEQ ID NO: 16, 150, 135	hsa-miR-455-3p, hsa-miR-1254, hsa-miR-7-1*	87.9 %	83.0 %	92.8 %
557	SEQ ID NO: 162, 157, 234	hsa-miR-142-5p, hsa-miR-566, hsa-miR-498	87.9 %	86.2 %	89.6 %
558	SEQ ID NO: 70, 52, 15	hsa-miR-1250, hsa-miR-802, hsa-miR-892b	87.9 %	96.6 %	79.2 %
559	SEQ ID NO: 52, 157, 137	hsa-miR-802, hsa-miR-566, hsa-miR-920	87.9 %	95.4 %	80.4 %
560	SEQ ID NO: 52, 243, 68	hsa-miR-802, hsa-miR-151-5p, hsa-miR-23b*	87.8 %	86.0 %	89.6 %
561	SEQ ID NO: 244, 135, 254	hsa-miR-874, hsa-miR-7-1*, hsa-miR-323-3p	87.8 %	85.6 %	90.0 %
562	SEQ ID NO: 254, 71, 35	hsa-miR-323-3p, hsa-miR-30e, hsa-miR-188-3p	87.8 %	93.8 %	81.8 %
563	SEQ ID NO: 184, 68, 16	hsa-miR-492, hsa-miR-23b*, hsa-miR-455-3p	87.8 %	95.2 %	80.4 %
564	SEQ ID NO: 137, 52, 15	hsa-miR-920, hsa-miR-802, hsa-miR-892b	87.8 %	99.8 %	75.8 %
565	SEQ ID NO: 15, 243, 123	hsa-miR-892b, hsa-miR-151-5p, hsa-miR-146b-3p	87.8 %	94.0 %	81.6 %

EP 2 865 765 A1

566	SEQ ID NO: 184, 16, 70	hsa-miR-492, hsa-miR-455-3p, hsa-miR-1250	87.8 %	90.0 %	85.6 %
567	SEQ ID NO: 184, 16, 252	hsa-miR-492, hsa-miR-455-3p, hsa-miR-497*	87.8 %	95.0 %	80.6 %
568	SEQ ID NO: 266, 231, 269	hsa-miR-615-5p, hsa-miR-93, hsa-miR-105	87.8 %	86.8 %	88.8 %
569	SEQ ID NO: 16, 70, 52	hsa-miR-455-3p, hsa-miR-1250, hsa-miR-802	87.8 %	95.6 %	80.0 %
570	SEQ ID NO: 162, 135, 71	hsa-miR-142-5p, hsa-miR-7-1*, hsa-miR-30e	87.7 %	93.0 %	82.4 %
571	SEQ ID NO: 252, 52, 15	hsa-miR-497*, hsa-miR-802, hsa-miR-892b	87.7 %	100.0 %	75.4 %
572	SEQ ID NO: 269, 243, 19	hsa-miR-105, hsa-miR-151-5p, hsa-miR-767-5p	87.7 %	94.0 %	81.4 %
573	SEQ ID NO: 135, 254, 255	hsa-miR-7-1*, hsa-miR-323-3p, hsa-miR-193a-3p	87.6 %	90.2 %	85.0 %
574	SEQ ID NO: 242, 243, 259	hsa-let-7i, hsa-miR-151-5p, hsa-miR-631	87.6 %	90.0 %	85.2 %
575	SEQ ID NO: 234, 184, 68	hsa-miR-498, hsa-miR-492, hsa-miR-23b*	87.6 %	85.6 %	89.6 %
576	SEQ ID NO: 257, 157, 234	hsa-miR-663b, hsa-miR-566, hsa-miR-498	87.6 %	84.4 %	90.8 %
577	SEQ ID NO: 266, 22, 269	hsa-miR-615-5p, hsa-miR-20b*, hsa-miR-105	87.6 %	93.6 %	81.6 %
578	SEQ ID NO: 184, 70, 266	hsa-miR-492, hsa-miR-1250, hsa-miR-615-5p	87.6 %	94.0 %	81.2 %
579	SEQ ID NO: 167, 242, 259	hsa-miR-627, hsa-let-7i, hsa-miR-631	87.5 %	85.0 %	90.0 %
580	SEQ ID NO: 243, 62, 95	hsa-miR-151-5p, hsa-miR-1281, hsa-miR-135b*	87.5 %	89.0 %	86.0 %
581	SEQ ID NO: 52, 243, 123	hsa-miR-802, hsa-miR-151-5p, hsa-miR-146b-3p	87.5 %	90.0 %	85.0 %
582	SEQ ID NO: 137, 184, 70	hsa-miR-920, hsa-miR-492, hsa-miR-1250	87.5 %	89.8 %	85.2 %
583	SEQ ID NO: 269, 243, 135	hsa-miR-105, hsa-miR-151-5p, hsa-miR-7-1*	87.5 %	95.0 %	80.0 %
584	SEQ ID NO: 62, 184, 68	hsa-miR-1281, hsa-miR-492, hsa-miR-23b*	87.4 %	94.8 %	80.0 %
585	SEQ ID NO: 157, 15, 123	hsa-miR-566, hsa-miR-892b, hsa-miR-146b-3p	87.4 %	99.6 %	75.2 %
586	SEQ ID NO: 252, 62, 16	hsa-miR-497*, hsa-miR-1281, hsa-miR-455-3p	87.4 %	94.8 %	80.0 %
587	SEQ ID NO: 242, 259, 125	hsa-let-7i, hsa-miR-631, hsa-miR-1285	87.4 %	85.0 %	89.8 %
588	SEQ ID NO: 253, 71, 255	hsa-miR-345, hsa-miR-30e, hsa-miR-193a-3p	87.4 %	90.4 %	84.4 %
589	SEQ ID NO: 257, 162, 234	hsa-miR-663b, hsa-miR-142-5p, hsa-miR-498	87.4 %	86.6 %	88.2 %
590	SEQ ID NO: 70, 137, 15	hsa-miR-1250, hsa-miR-920, hsa-miR-892b	87.4 %	98.8 %	76.0 %
591	SEQ ID NO: 184, 70, 265	hsa-miR-492, hsa-miR-1250, hsa-miR-129-5p	87.4 %	89.8 %	85.0 %
592	SEQ ID NO: 252, 62, 184	hsa-miR-497*, hsa-miR-1281, hsa-miR-492	87.3 %	90.8 %	83.8 %
593	SEQ ID NO: 71, 85, 255	hsa-miR-30e, hsa-miR-140-5p, hsa-miR-193a-3p	87.3 %	86.4 %	88.2 %
594	SEQ ID NO: 70, 32, 150	hsa-miR-1250, hsa-miR-380*, hsa-miR-1254	87.3 %	87.8 %	86.8 %
595	SEQ ID NO: 135, 19, 16	hsa-miR-7-1*, hsa-miR-767-5p, hsa-miR-455-3p	87.3 %	81.2 %	93.4 %
596	SEQ ID NO: 257, 123, 156	hsa-miR-663b, hsa-miR-146b-3p, hsa-miR-217	87.3 %	96.8 %	77.8 %
597	SEQ ID NO: 242, 243,	hsa-let-7i, hsa-miR-151-5p, hsa-miR-1285	87.2	90.0	84.4

EP 2 865 765 A1

	125		%	%	%
598	SEQ ID NO: 266, 24, 22	hsa-miR-615-5p, hsa-miR-330-3p, hsa-miR-20b*	87.2 %	91.0 %	83.4 %
599	SEQ ID NO: 243, 95, 150	hsa-miR-151-5p, hsa-miR-135b*, hsa-miR-1254	87.2 %	79.2 %	95.2 %
600	SEQ ID NO: 265, 257, 123	hsa-miR-129-5p, hsa-miR-663b, hsa-miR-146b-3p	87.2 %	89.6 %	84.8 %
601	SEQ ID NO: 62, 243, 68	hsa-miR-1281, hsa-miR-151-5p, hsa-miR-23b*	87.0 %	93.2 %	80.8 %
602	SEQ ID NO: 16, 252, 52	hsa-miR-455-3p, hsa-miR-497*, hsa-miR-802	87.0 %	94.0 %	80.0 %
603	SEQ ID NO: 234, 16, 70	hsa-miR-498, hsa-miR-455-3p, hsa-miR-1250	87.0 %	93.4 %	80.6 %
604	SEQ ID NO: 52, 157, 162	hsa-miR-802, hsa-miR-566, hsa-miR-142-5p	87.0 %	93.0 %	81.0 %
605	SEQ ID NO: 70, 266, 257	hsa-miR-1250, hsa-miR-615-5p, hsa-miR-663b	87.0 %	94.6 %	79.4 %
606	SEQ ID NO: 265, 150, 123	hsa-miR-129-5p, hsa-miR-1254, hsa-miR-146b-3p	87.0 %	90.2 %	83.8 %
607	SEQ ID NO: 22, 31, 16	hsa-miR-20b*, hsa-miR-139-5p, hsa-miR-455-3p	87.0 %	85.0 %	89.0 %
608	SEQ ID NO: 150, 157, 253	hsa-miR-1254, hsa-miR-566, hsa-miR-345	86.9 %	94.0 %	79.8 %
609	SEQ ID NO: 157, 31, 123	hsa-miR-566, hsa-miR-139-5p, hsa-miR-146b-3p	86.9 %	95.0 %	78.8 %
610	SEQ ID NO: 259, 150, 253	hsa-miR-631, hsa-miR-1254, hsa-miR-345	86.9 %	83.4 %	90.4 %
611	SEQ ID NO: 231, 22, 32	hsa-miR-93, hsa-miR-20b*, hsa-miR-380*	86.9 %	84.2 %	89.6 %
612	SEQ ID NO: 135, 16, 32	hsa-miR-7-1*, hsa-miR-455-3p, hsa-miR-380*	86.9 %	75.2 %	98.6 %
613	SEQ ID NO: 15, 123, 174	hsa-miR-892b, hsa-miR-146b-3p, hsa-miR-636	86.8 %	98.2 %	75.4 %
614	SEQ ID NO: 123, 244, 135	hsa-miR-146b-3p, hsa-miR-874, hsa-miR-7-1*	86.8 %	95.8 %	77.8 %
615	SEQ ID NO: 123, 150, 265	hsa-miR-146b-3p, hsa-miR-1254, hsa-miR-129-5p	86.8 %	90.0 %	83.6 %
616	SEQ ID NO: 266, 150, 15	hsa-miR-615-5p, hsa-miR-1254, hsa-miR-892b	86.8 %	89.6 %	84.0 %
617	SEQ ID NO: 135, 254, 85	hsa-miR-7-1*, hsa-miR-323-3p, hsa-miR-140-5p	86.7 %	77.8 %	95.6 %
618	SEQ ID NO: 15, 22, 244	hsa-miR-892b, hsa-miR-20b*, hsa-miR-874	86.7 %	89.8 %	83.6 %
619	SEQ ID NO: 70, 32, 95	hsa-miR-1250, hsa-miR-380*, hsa-miR-135b*	86.7 %	92.0 %	81.4 %
620	SEQ ID NO: 95, 157, 15	hsa-miR-135b*, hsa-miR-566, hsa-miR-892b	86.7 %	94.8 %	78.6 %
621	SEQ ID NO: 252, 137, 52	hsa-miR-497*, hsa-miR-920, hsa-miR-802	86.7 %	98.4 %	75.0 %
622	SEQ ID NO: 257, 123, 95	hsa-miR-663b, hsa-miR-146b-3p, hsa-miR-135b*	86.7 %	93.8 %	79.6 %
623	SEQ ID NO: 157, 253, 31	hsa-miR-566, hsa-miR-345, hsa-miR-139-5p	86.6 %	90.0 %	83.2 %
624	SEQ ID NO: 259, 157, 253	hsa-miR-631, hsa-miR-566, hsa-miR-345	86.6 %	83.6 %	89.6 %
625	SEQ ID NO: 24, 22, 32	hsa-miR-330-3p, hsa-miR-20b*, hsa-miR-380*	86.6 %	83.2 %	90.0 %
626	SEQ ID NO: 266, 257, 15	hsa-miR-615-5p, hsa-miR-663b, hsa-miR-892b	86.6 %	93.4 %	79.8 %
627	SEQ ID NO: 22, 244, 135	hsa-miR-20b*, hsa-miR-874, hsa-miR-7-1*	86.5 %	89.8 %	83.2 %
628	SEQ ID NO: 217, 252, 62	hsa-miR-148b, hsa-miR-497*, hsa-miR-1281	86.5 %	93.6 %	79.4 %

EP 2 865 765 A1

629	SEQ ID NO: 156, 266, 24	hsa-miR-217, hsa-miR-615-5p, hsa-miR-330-3p	86.5 %	93.0 %	80.0 %
630	SEQ ID NO: 22, 269, 32	hsa-miR-20b*, hsa-miR-105, hsa-miR-380*	86.5 %	84.4 %	88.6 %
631	SEQ ID NO: 231, 32, 232	hsa-miR-93, hsa-miR-380*, hsa-miR-624	86.5 %	84.6 %	88.4 %
632	SEQ ID NO: 242, 244, 125	hsa-let-7i, hsa-miR-874, hsa-miR-1285	86.4 %	83.6 %	89.2 %
633	SEQ ID NO: 242, 243, 231	hsa-let-7i, hsa-miR-151-5p, hsa-miR-93	86.4 %	83.4 %	89.4 %
634	SEQ ID NO: 252, 52, 243	hsa-miR-497*, hsa-miR-802, hsa-miR-151-5p	86.3 %	87.6 %	85.0 %
635	SEQ ID NO: 243, 259, 125	hsa-miR-151-5p, hsa-miR-631, hsa-miR-1285	86.2 %	85.4 %	87.0 %
636	SEQ ID NO: 184, 266, 265	hsa-miR-492, hsa-miR-615-5p, hsa-miR-129-5p	86.2 %	88.4 %	84.0 %
637	SEQ ID NO: 68, 70, 32	hsa-miR-23b*, hsa-miR-1250, hsa-miR-380*	86.1 %	89.0 %	83.2 %
638	SEQ ID NO: 243, 22, 19	hsa-miR-151-5p, hsa-miR-20b*, hsa-miR-767-5p	86.1 %	83.0 %	89.2 %
639	SEQ ID NO: 162, 266, 150	hsa-miR-142-5p, hsa-miR-615-5p, hsa-miR-1254	86.1 %	86.4 %	85.8 %
640	SEQ ID NO: 68, 70, 259	hsa-miR-23b*, hsa-miR-1250, hsa-miR-631	86.0 %	92.4 %	79.6 %
641	SEQ ID NO: 259, 95, 253	hsa-miR-631, hsa-miR-135b*, hsa-miR-345	86.0 %	82.0 %	90.0 %
642	SEQ ID NO: 31, 123, 174	hsa-miR-139-5p, hsa-miR-146b-3p, hsa-miR-636	86.0 %	94.8 %	77.2 %
643	SEQ ID NO: 150, 266, 24	hsa-miR-1254, hsa-miR-615-5p, hsa-miR-330-3p	86.0 %	92.0 %	80.0 %
644	SEQ ID NO: 31, 15, 123	hsa-miR-139-5p, hsa-miR-892b, hsa-miR-146b-3p	85.9 %	96.8 %	75.0 %
645	SEQ ID NO: 52, 68, 70	hsa-miR-802, hsa-miR-23b*, hsa-miR-1250	85.9 %	91.8 %	80.0 %
646	SEQ ID NO: 32, 273, 24	hsa-miR-380*, hsa-miR-194*, hsa-miR-330-3p	85.9 %	85.8 %	86.0 %
647	SEQ ID NO: 27, 217, 62	hsa-miR-423-5p, hsa-miR-148b, hsa-miR-1281	85.8 %	86.0 %	85.6 %
648	SEQ ID NO: 27, 252, 62	hsa-miR-423-5p, hsa-miR-497*, hsa-miR-1281	85.8 %	92.4 %	79.2 %
649	SEQ ID NO: 242, 259, 244	hsa-let-7i, hsa-miR-631, hsa-miR-874	85.8 %	77.8 %	93.8 %
650	SEQ ID NO: 70, 265, 257	hsa-miR-1250, hsa-miR-129-5p, hsa-miR-663b	85.8 %	86.0 %	85.6 %
651	SEQ ID NO: 265, 15, 123	hsa-miR-129-5p, hsa-miR-892b, hsa-miR-146b-3p	85.8 %	89.2 %	82.4 %
652	SEQ ID NO: 95, 253, 31	hsa-miR-135b*, hsa-miR-345, hsa-miR-139-5p	85.7 %	85.4 %	86.0 %
653	SEQ ID NO: 244, 254, 85	hsa-miR-874, hsa-miR-323-3p, hsa-miR-140-5p	85.7 %	79.6 %	91.8 %
654	SEQ ID NO: 162, 234, 184	hsa-miR-142-5p, hsa-miR-498, hsa-miR-492	85.7 %	85.8 %	85.6 %
655	SEQ ID NO: 252, 137, 15	hsa-miR-497*, hsa-miR-920, hsa-miR-892b	85.7 %	95.6 %	75.8 %
656	SEQ ID NO: 70, 137, 52	hsa-miR-1250, hsa-miR-920, hsa-miR-802	85.7 %	90.8 %	80.6 %
657	SEQ ID NO: 243, 135, 31	hsa-miR-151-5p, hsa-miR-7-1*, hsa-miR-139-5p	85.7 %	86.0 %	85.4 %
658	SEQ ID NO: 32, 95, 157	hsa-miR-380*, hsa-miR-135b*, hsa-miR-566	85.6 %	96.2 %	75.0 %
659	SEQ ID NO: 15, 123, 22	hsa-miR-892b, hsa-miR-146b-3p, hsa-miR-20b*	85.5 %	94.0 %	77.0 %
660	SEQ ID NO: 22, 174, 135	hsa-miR-20b*, hsa-miR-636, hsa-miR-7-	85.5 %	81.0 %	90.0 %

EP 2 865 765 A1

		1*	%	%	%
661	SEQ ID NO: 16, 174, 135	hsa-miR-455-3p, hsa-miR-636, hsa-miR-7-1*	85.5 %	80.0 %	91.0 %
662	SEQ ID NO: 70, 252, 137	hsa-miR-1250, hsa-miR-497*, hsa-miR-920	85.5 %	91.0 %	80.0 %
663	SEQ ID NO: 24, 231, 22	hsa-miR-330-3p, hsa-miR-93, hsa-miR-20b*	85.5 %	87.6 %	83.4 %
664	SEQ ID NO: 16, 32, 252	hsa-miR-455-3p, hsa-miR-380*, hsa-miR-497*	85.5 %	86.0 %	85.0 %
665	SEQ ID NO: 174, 135, 254	hsa-miR-636, hsa-miR-7-1*, hsa-miR-323-3p	85.4 %	80.4 %	90.4 %
666	SEQ ID NO: 123, 22, 135	hsa-miR-146b-3p, hsa-miR-20b*, hsa-miR-7-1*	85.4 %	83.0 %	87.8 %
667	SEQ ID NO: 31, 32, 273	hsa-miR-139-5p, hsa-miR-380*, hsa-miR-194*	85.4 %	90.4 %	80.4 %
668	SEQ ID NO: 184, 162, 265	hsa-miR-492, hsa-miR-142-5p, hsa-miR-129-5p	85.4 %	85.4 %	85.4 %
669	SEQ ID NO: 31, 273, 252	hsa-miR-139-5p, hsa-miR-194*, hsa-miR-497*	85.4 %	100.0 %	70.8 %
670	SEQ ID NO: 71, 255, 24	hsa-miR-30e, hsa-miR-193a-3p, hsa-miR-330-3p	85.3 %	85.2 %	85.4 %
671	SEQ ID NO: 70, 150, 257	hsa-miR-1250, hsa-miR-1254, hsa-miR-663b	85.3 %	91.8 %	78.8 %
672	SEQ ID NO: 184, 243, 68	hsa-miR-492, hsa-miR-151-5p, hsa-miR-23b*	85.2 %	85.8 %	84.6 %
673	SEQ ID NO: 70, 150, 95	hsa-miR-1250, hsa-miR-1254, hsa-miR-135b*	85.2 %	91.8 %	78.6 %
674	SEQ ID NO: 250, 27, 217	hsa-miR-374a, hsa-miR-423-5p, hsa-miR-148b	85.2 %	84.8 %	85.6 %
675	SEQ ID NO: 252, 16, 150	hsa-miR-497*, hsa-miR-455-3p, hsa-miR-1254	85.2 %	90.4 %	80.0 %
676	SEQ ID NO: 255, 35, 242	hsa-miR-193a-3p, hsa-miR-188-3p, hsa-let-7i	85.2 %	85.6 %	84.8 %
677	SEQ ID NO: 16, 252, 137	hsa-miR-455-3p, hsa-miR-497*, hsa-miR-920	85.2 %	89.0 %	81.4 %
678	SEQ ID NO: 70, 266, 265	hsa-miR-1250, hsa-miR-615-5p, hsa-miR-129-5p	85.2 %	89.2 %	81.2 %
679	SEQ ID NO: 19, 32, 273	hsa-miR-767-5p, hsa-miR-380*, hsa-miR-194*	85.2 %	88.6 %	81.8 %
680	SEQ ID NO: 31, 22, 174	hsa-miR-139-5p, hsa-miR-20b*, hsa-miR-636	85.1 %	87.6 %	82.6 %
681	SEQ ID NO: 217, 116, 16	hsa-miR-148b, hsa-miR-339-3p, hsa-miR-455-3p	85.1 %	81.6 %	88.6 %
682	SEQ ID NO: 135, 255, 35	hsa-miR-7-1*, hsa-miR-193a-3p, hsa-miR-188-3p	85.1 %	85.2 %	85.0 %
683	SEQ ID NO: 156, 24, 22	hsa-miR-217, hsa-miR-330-3p, hsa-miR-20b*	85.1 %	85.6 %	84.6 %
684	SEQ ID NO: 135, 255, 24	hsa-miR-7-1*, hsa-miR-193a-3p, hsa-miR-330-3p	85.0 %	86.0 %	84.0 %
685	SEQ ID NO: 253, 174, 255	hsa-miR-345, hsa-miR-636, hsa-miR-193a-3p	85.0 %	89.8 %	80.2 %
686	SEQ ID NO: 123, 95, 156	hsa-miR-146b-3p, hsa-miR-135b*, hsa-miR-217	85.0 %	95.4 %	74.6 %
687	SEQ ID NO: 71, 85, 35	hsa-miR-30e, hsa-miR-140-5p, hsa-miR-188-3p	84.9 %	85.6 %	84.2 %
688	SEQ ID NO: 116, 252, 62	hsa-miR-339-3p, hsa-miR-497*, hsa-miR-1281	84.9 %	89.8 %	80.0 %
689	SEQ ID NO: 255, 24, 167	hsa-miR-193a-3p, hsa-miR-330-3p, hsa-miR-627	84.9 %	89.6 %	80.2 %
690	SEQ ID NO: 24, 22, 269	hsa-miR-330-3p, hsa-miR-20b*, hsa-miR-105	84.9 %	92.4 %	77.4 %
691	SEQ ID NO: 269, 135, 71	hsa-miR-105, hsa-miR-7-1*, hsa-miR-30e	84.9 %	90.0 %	79.8 %

EP 2 865 765 A1

692	SEQ ID NO: 150, 253, 135	hsa-miR-1254, hsa-miR-345, hsa-miR-7-1*	84.8 %	90.0 %	79.6 %
693	SEQ ID NO: 16, 70, 137	hsa-miR-455-3p, hsa-miR-1250, hsa-miR-920	84.8 %	82.2 %	87.4 %
694	SEQ ID NO: 257, 15, 95	hsa-miR-663b, hsa-miR-892b, hsa-miR-135b*	84.8 %	94.4 %	75.2 %
695	SEQ ID NO: 137, 184, 266	hsa-miR-920, hsa-miR-492, hsa-miR-615-5p	84.8 %	94.8 %	74.8 %
696	SEQ ID NO: 157, 253, 15	hsa-miR-566, hsa-miR-345, hsa-miR-892b	84.7 %	85.2 %	84.2 %
697	SEQ ID NO: 253, 31, 22	hsa-miR-345, hsa-miR-139-5p, hsa-miR-20b*	84.7 %	83.8 %	85.6 %
698	SEQ ID NO: 265, 156, 24	hsa-miR-129-5p, hsa-miR-217, hsa-miR-330-3p	84.7 %	84.4 %	85.0 %
699	SEQ ID NO: 265, 266, 231	hsa-miR-129-5p, hsa-miR-615-5p, hsa-miR-93	84.7 %	84.4 %	85.0 %
700	SEQ ID NO: 254, 85, 255	hsa-miR-323-3p, hsa-miR-140-5p, hsa-miR-193a-3p	84.6 %	84.6 %	84.6 %
701	SEQ ID NO: 217, 116, 62	hsa-miR-148b, hsa-miR-339-3p, hsa-miR-1281	84.6 %	86.2 %	83.0 %
702	SEQ ID NO: 174, 135, 35	hsa-miR-636, hsa-miR-7-1*, hsa-miR-188-3p	84.6 %	79.8 %	89.4 %
703	SEQ ID NO: 123, 95, 265	hsa-miR-146b-3p, hsa-miR-135b*, hsa-miR-129-5p	84.6 %	89.2 %	80.0 %
704	SEQ ID NO: 15, 123, 95	hsa-miR-892b, hsa-miR-146b-3p, hsa-miR-135b*	84.6 %	99.0 %	70.2 %
705	SEQ ID NO: 31, 32, 252	hsa-miR-139-5p, hsa-miR-380*, hsa-miR-497*	84.6 %	90.0 %	79.2 %
706	SEQ ID NO: 32, 150, 157	hsa-miR-380*, hsa-miR-1254, hsa-miR-566	84.5 %	84.6 %	84.4 %
707	SEQ ID NO: 52, 243, 70	hsa-miR-802, hsa-miR-151-5p, hsa-miR-1250	84.5 %	84.0 %	85.0 %
708	SEQ ID NO: 242, 244, 231	hsa-let-7i, hsa-miR-874, hsa-miR-93	84.5 %	79.4 %	89.6 %
709	SEQ ID NO: 255, 35, 24	hsa-miR-193a-3p, hsa-miR-188-3p, hsa-miR-330-3p	84.5 %	92.0 %	77.0 %
710	SEQ ID NO: 24, 231, 32	hsa-miR-330-3p, hsa-miR-93, hsa-miR-380*	84.5 %	77.8 %	91.2 %
711	SEQ ID NO: 32, 259, 150	hsa-miR-380*, hsa-miR-631, hsa-miR-1254	84.4 %	80.4 %	88.4 %
712	SEQ ID NO: 31, 15, 22	hsa-miR-139-5p, hsa-miR-892b, hsa-miR-20b*	84.4 %	93.8 %	75.0 %
713	SEQ ID NO: 150, 157, 31	hsa-miR-1254, hsa-miR-566, hsa-miR-139-5p	84.4 %	89.0 %	79.8 %
714	SEQ ID NO: 135, 71, 255	hsa-miR-7-1*, hsa-miR-30e, hsa-miR-193a-3p	84.4 %	80.4 %	88.4 %
715	SEQ ID NO: 174, 244, 71	hsa-miR-636, hsa-miR-874, hsa-miR-30e	84.4 %	79.8 %	89.0 %
716	SEQ ID NO: 251, 217, 252	hsa-miR-182, hsa-miR-148b, hsa-miR-497*	84.3 %	87.2 %	81.4 %
717	SEQ ID NO: 266, 24, 231	hsa-miR-615-5p, hsa-miR-330-3p, hsa-miR-93	84.3 %	89.4 %	79.2 %
718	SEQ ID NO: 135, 19, 31	hsa-miR-7-1*, hsa-miR-767-5p, hsa-miR-139-5p	84.3 %	74.6 %	94.0 %
719	SEQ ID NO: 32, 273, 23	hsa-miR-380*, hsa-miR-194*, hsa-miR-491-3p	84.3 %	89.0 %	79.6 %
720	SEQ ID NO: 135, 19, 32	hsa-miR-7-1*, hsa-miR-767-5p, hsa-miR-380*	84.3 %	74.8 %	93.8 %
721	SEQ ID NO: 135, 24, 242	hsa-miR-7-1*, hsa-miR-330-3p, hsa-let-7i	84.2 %	79.6 %	88.8 %
722	SEQ ID NO: 66, 245, 155	hsa-miR-1295, hsa-miR-106a, hsa-miR-484	84.2 %	86.2 %	82.2 %
723	SEQ ID NO: 269, 232,	hsa-miR-105, hsa-miR-624, hsa-miR-7-1*	84.2 %	92.8 %	75.6 %

EP 2 865 765 A1

	135		%	%	%
724	SEQ ID NO: 22, 135, 19	hsa-miR-20b*, hsa-miR-7-1*, hsa-miR-767-5p	84.2 %	74.8 %	93.6 %
725	SEQ ID NO: 16, 32, 150	hsa-miR-455-3p, hsa-miR-380*, hsa-miR-1254	84.1 %	79.4 %	88.8 %
726	SEQ ID NO: 35, 24, 242	hsa-miR-188-3p, hsa-miR-330-3p, hsa-let-7i	84.1 %	80.4 %	87.8 %
727	SEQ ID NO: 257, 95, 156	hsa-miR-663b, hsa-miR-135b*, hsa-miR-217	84.1 %	94.0 %	74.2 %
728	SEQ ID NO: 32, 150, 95	hsa-miR-380*, hsa-miR-1254, hsa-miR-135b*	84.0 %	88.2 %	79.8 %
729	SEQ ID NO: 15, 174, 244	hsa-miR-892b, hsa-miR-636, hsa-miR-874	84.0 %	90.6 %	77.4 %
730	SEQ ID NO: 156, 269, 135	hsa-miR-217, hsa-miR-105, hsa-miR-7-1*	84.0 %	88.6 %	79.4 %
731	SEQ ID NO: 31, 16, 252	hsa-miR-139-5p, hsa-miR-455-3p, hsa-miR-497*	84.0 %	94.4 %	73.6 %
732	SEQ ID NO: 123, 22, 244	hsa-miR-146b-3p, hsa-miR-20b*, hsa-miR-874	83.9 %	81.8 %	86.0 %
733	SEQ ID NO: 68, 32, 259	hsa-miR-23b*, hsa-miR-380*, hsa-miR-631	83.9 %	92.0 %	75.8 %
734	SEQ ID NO: 162, 71, 242	hsa-miR-142-5p, hsa-miR-30e, hsa-let-7i	83.8 %	84.8 %	82.8 %
735	SEQ ID NO: 27, 217, 252	hsa-miR-423-5p, hsa-miR-148b, hsa-miR-497*	83.7 %	83.8 %	83.6 %
736	SEQ ID NO: 35, 167, 242	hsa-miR-188-3p, hsa-miR-627, hsa-let-7i	83.7 %	77.6 %	89.8 %
737	SEQ ID NO: 255, 24, 242	hsa-miR-193a-3p, hsa-miR-330-3p, hsa-let-7i	83.7 %	82.4 %	85.0 %
738	SEQ ID NO: 255, 167, 242	hsa-miR-193a-3p, hsa-miR-627, hsa-let-7i	83.7 %	87.4 %	80.0 %
739	SEQ ID NO: 231, 269, 232	hsa-miR-93, hsa-miR-105, hsa-miR-624	83.7 %	88.2 %	79.2 %
740	SEQ ID NO: 95, 156, 269	hsa-miR-135b*, hsa-miR-217, hsa-miR-105	83.7 %	85.0 %	82.4 %
741	SEQ ID NO: 266, 265, 15	hsa-miR-615-5p, hsa-miR-129-5p, hsa-miR-892b	83.7 %	89.6 %	77.8 %
742	SEQ ID NO: 70, 259, 95	hsa-miR-1250, hsa-miR-631, hsa-miR-135b*	83.6 %	87.2 %	80.0 %
743	SEQ ID NO: 243, 68, 32	hsa-miR-151-5p, hsa-miR-23b*, hsa-miR-380*	83.6 %	82.0 %	85.2 %
744	SEQ ID NO: 167, 242, 244	hsa-miR-627, hsa-let-7i, hsa-miR-874	83.6 %	74.2 %	93.0 %
745	SEQ ID NO: 150, 156, 24	hsa-miR-1254, hsa-miR-217, hsa-miR-330-3p	83.6 %	87.2 %	80.0 %
746	SEQ ID NO: 22, 32, 135	hsa-miR-20b*, hsa-miR-380*, hsa-miR-7-1*	83.6 %	78.2 %	89.0 %
747	SEQ ID NO: 257, 15, 123	hsa-miR-663b, hsa-miR-892b, hsa-miR-146b-3p	83.5 %	91.6 %	75.4 %
748	SEQ ID NO: 265, 257, 15	hsa-miR-129-5p, hsa-miR-663b, hsa-miR-892b	83.5 %	83.0 %	84.0 %
749	SEQ ID NO: 244, 125, 231	hsa-miR-874, hsa-miR-1285, hsa-miR-93	83.3 %	81.0 %	85.6 %
750	SEQ ID NO: 16, 70, 32	hsa-miR-455-3p, hsa-miR-1250, hsa-miR-380*	83.2 %	80.8 %	85.6 %
751	SEQ ID NO: 135, 71, 85	hsa-miR-7-1*, hsa-miR-30e, hsa-miR-140-5p	83.2 %	81.8 %	84.6 %
752	SEQ ID NO: 32, 259, 157	hsa-miR-380*, hsa-miR-631, hsa-miR-566	83.2 %	84.8 %	81.6 %
753	SEQ ID NO: 259, 244, 231	hsa-miR-631, hsa-miR-874, hsa-miR-93	83.2 %	84.4 %	82.0 %
754	SEQ ID NO: 167, 243, 259	hsa-miR-627, hsa-miR-151-5p, hsa-miR-631	83.2 %	84.8 %	81.6 %

EP 2 865 765 A1

755	SEQ ID NO: 150, 253, 71	hsa-miR-1254, hsa-miR-345, hsa-miR-30e	83.2 %	87.2 %	79.2 %
756	SEQ ID NO: 269, 243, 22	hsa-miR-105, hsa-miR-151-5p, hsa-miR-20b*	83.2 %	78.4 %	88.0 %
757	SEQ ID NO: 15, 95, 156	hsa-miR-892b, hsa-miR-135b*, hsa-miR-217	83.2 %	97.8 %	68.6 %
758	SEQ ID NO: 16, 150, 253	hsa-miR-455-3p, hsa-miR-1254, hsa-miR-345	83.1 %	85.6 %	80.6 %
759	SEQ ID NO: 257, 15, 156	hsa-miR-663b, hsa-miR-892b, hsa-miR-217	83.1 %	87.0 %	79.2 %
760	SEQ ID NO: 68, 16, 32	hsa-miR-23b*, hsa-miR-455-3p, hsa-miR-380*	83.0 %	85.8 %	80.2 %
761	SEQ ID NO: 71, 242, 243	hsa-miR-30e, hsa-let-7i, hsa-miR-151-5p	83.0 %	81.8 %	84.2 %
762	SEQ ID NO: 174, 135, 255	hsa-miR-636, hsa-miR-7-1*, hsa-miR-193a-3p	83.0 %	85.8 %	80.2 %
763	SEQ ID NO: 71, 255, 167	hsa-miR-30e, hsa-miR-193a-3p, hsa-miR-627	83.0 %	85.0 %	81.0 %
764	SEQ ID NO: 266, 231, 22	hsa-miR-615-5p, hsa-miR-93, hsa-miR-20b*	83.0 %	86.8 %	79.2 %
765	SEQ ID NO: 150, 257, 15	hsa-miR-1254, hsa-miR-663b, hsa-miR-892b	83.0 %	90.2 %	75.8 %
766	SEQ ID NO: 123, 174, 244	hsa-miR-146b-3p, hsa-miR-636, hsa-miR-874	82.9 %	83.8 %	82.0 %
767	SEQ ID NO: 135, 71, 24	hsa-miR-7-1*, hsa-miR-30e, hsa-miR-330-3p	82.9 %	79.8 %	86.0 %
768	SEQ ID NO: 59, 181, 12	hsa-miR-1301, hsa-miR-145, hsa-miR-128	82.9 %	92.0 %	73.8 %
769	SEQ ID NO: 269, 32, 135	hsa-miR-105, hsa-miR-380*, hsa-miR-7-1*	82.9 %	85.8 %	80.0 %
770	SEQ ID NO: 22, 19, 31	hsa-miR-20b*, hsa-miR-767-5p, hsa-miR-139-5p	82.9 %	87.4 %	78.4 %
771	SEQ ID NO: 70, 32, 259	hsa-miR-1250, hsa-miR-380*, hsa-miR-631	82.8 %	84.8 %	80.8 %
772	SEQ ID NO: 95, 157, 253	hsa-miR-135b*, hsa-miR-566, hsa-miR-345	82.8 %	88.2 %	77.4 %
773	SEQ ID NO: 253, 135, 255	hsa-miR-345, hsa-miR-7-1*, hsa-miR-193a-3p	82.8 %	86.4 %	79.2 %
774	SEQ ID NO: 71, 35, 167	hsa-miR-30e, hsa-miR-188-3p, hsa-miR-627	82.8 %	81.2 %	84.4 %
775	SEQ ID NO: 269, 32, 232	hsa-miR-105, hsa-miR-380*, hsa-miR-624	82.8 %	87.2 %	78.4 %
776	SEQ ID NO: 269, 22, 19	hsa-miR-105, hsa-miR-20b*, hsa-miR-767-5p	82.8 %	85.6 %	80.0 %
777	SEQ ID NO: 95, 156, 22	hsa-miR-135b*, hsa-miR-217, hsa-miR-20b*	82.8 %	86.0 %	79.6 %
778	SEQ ID NO: 135, 71, 35	hsa-miR-7-1*, hsa-miR-30e, hsa-miR-188-3p	82.7 %	80.8 %	84.6 %
779	SEQ ID NO: 71, 35, 24	hsa-miR-30e, hsa-miR-188-3p, hsa-miR-330-3p	82.7 %	84.8 %	80.6 %
780	SEQ ID NO: 150, 15, 95	hsa-miR-1254, hsa-miR-892b, hsa-miR-135b*	82.7 %	93.0 %	72.4 %
781	SEQ ID NO: 254, 255, 35	hsa-miR-323-3p, hsa-miR-193a-3p, hsa-miR-188-3p	82.6 %	84.0 %	81.2 %
782	SEQ ID NO: 246, 181, 248	hsa-miR-20a, hsa-miR-145, hsa-let-7b	82.6 %	89.8 %	75.4 %
783	SEQ ID NO: 174, 71, 255	hsa-miR-636, hsa-miR-30e, hsa-miR-193a-3p	82.6 %	78.6 %	86.6 %
784	SEQ ID NO: 95, 31, 15	hsa-miR-135b*, hsa-miR-139-5p, hsa-miR-892b	82.5 %	90.4 %	74.6 %
785	SEQ ID NO: 32, 252, 23	hsa-miR-380*, hsa-miR-497*, hsa-miR-491-3p	82.5 %	85.0 %	80.0 %
786	SEQ ID NO: 157, 31, 15	hsa-miR-566, hsa-miR-139-5p, hsa-miR-	82.4 %	89.4 %	75.4 %

EP 2 865 765 A1

		892b	%	%	%
787	SEQ ID NO: 71, 255, 35	hsa-miR-30e, hsa-miR-193a-3p, hsa-miR-188-3p	82.4 %	83.8 %	81.0 %
788	SEQ ID NO: 31, 15, 174	hsa-miR-139-5p, hsa-miR-892b, hsa-miR-636	82.3 %	89.6 %	75.0 %
789	SEQ ID NO: 16, 253, 135	hsa-miR-455-3p, hsa-miR-345, hsa-miR-7-1*	82.3 %	85.2 %	79.4 %
790	SEQ ID NO: 24, 269, 32	hsa-miR-330-3p, hsa-miR-105, hsa-miR-380*	82.3 %	76.4 %	88.2 %
791	SEQ ID NO: 95, 243, 22	hsa-miR-135b*, hsa-miR-151-5p, hsa-miR-20b*	82.3 %	75.0 %	89.6 %
792	SEQ ID NO: 71, 24, 242	hsa-miR-30e, hsa-miR-330-3p, hsa-let-7i	82.2 %	74.6 %	89.8 %
793	SEQ ID NO: 16, 70, 252	hsa-miR-455-3p, hsa-miR-1250, hsa-miR-497*	82.2 %	86.0 %	78.4 %
794	SEQ ID NO: 123, 150, 156	hsa-miR-146b-3p, hsa-miR-1254, hsa-miR-217	82.2 %	89.0 %	75.4 %
795	SEQ ID NO: 259, 150, 95	hsa-miR-631, hsa-miR-1254, hsa-miR-135b*	82.1 %	85.2 %	79.0 %
796	SEQ ID NO: 85, 255, 35	hsa-miR-140-5p, hsa-miR-193a-3p, hsa-miR-188-3p	82.1 %	95.0 %	69.2 %
797	SEQ ID NO: 70, 259, 150	hsa-miR-1250, hsa-miR-631, hsa-miR-1254	82.1 %	79.8 %	84.4 %
798	SEQ ID NO: 24, 244, 125	hsa-miR-330-3p, hsa-miR-874, hsa-miR-1285	82.1 %	74.8 %	89.4 %
799	SEQ ID NO: 24, 231, 269	hsa-miR-330-3p, hsa-miR-93, hsa-miR-105	82.1 %	80.6 %	83.6 %
800	SEQ ID NO: 19, 31, 16	hsa-miR-767-5p, hsa-miR-139-5p, hsa-miR-455-3p	82.1 %	87.6 %	76.6 %
801	SEQ ID NO: 156, 269, 22	hsa-miR-217, hsa-miR-105, hsa-miR-20b*	82.1 %	80.2 %	84.0 %
802	SEQ ID NO: 19, 16, 32	hsa-miR-767-5p, hsa-miR-455-3p, hsa-miR-380*	82.1 %	79.6 %	84.6 %
803	SEQ ID NO: 16, 32, 259	hsa-miR-455-3p, hsa-miR-380*, hsa-miR-631	82.0 %	78.8 %	85.2 %
804	SEQ ID NO: 116, 252, 16	hsa-miR-339-3p, hsa-miR-497*, hsa-miR-455-3p	82.0 %	86.6 %	77.4 %
805	SEQ ID NO: 232, 135, 71	hsa-miR-624, hsa-miR-7-1*, hsa-miR-30e	82.0 %	88.8 %	75.2 %
806	SEQ ID NO: 16, 259, 150	hsa-miR-455-3p, hsa-miR-631, hsa-miR-1254	81.9 %	76.2 %	87.6 %
807	SEQ ID NO: 22, 135, 254	hsa-miR-20b*, hsa-miR-7-1*, hsa-miR-323-3p	81.9 %	70.0 %	93.8 %
808	SEQ ID NO: 150, 265, 24	hsa-miR-1254, hsa-miR-129-5p, hsa-miR-330-3p	81.9 %	82.8 %	81.0 %
809	SEQ ID NO: 244, 71, 85	hsa-miR-874, hsa-miR-30e, hsa-miR-140-5p	81.8 %	77.8 %	85.8 %
810	SEQ ID NO: 253, 135, 71	hsa-miR-345, hsa-miR-7-1*, hsa-miR-30e	81.8 %	86.4 %	77.2 %
811	SEQ ID NO: 273, 252, 24	hsa-miR-194*, hsa-miR-497*, hsa-miR-330-3p	81.8 %	89.6 %	74.0 %
812	SEQ ID NO: 150, 95, 253	hsa-miR-1254, hsa-miR-135b*, hsa-miR-345	81.7 %	78.6 %	84.8 %
813	SEQ ID NO: 259, 244, 125	hsa-miR-631, hsa-miR-874, hsa-miR-1285	81.7 %	89.0 %	74.4 %
814	SEQ ID NO: 243, 22, 31	hsa-miR-151-5p, hsa-miR-20b*, hsa-miR-139-5p	81.7 %	74.8 %	88.6 %
815	SEQ ID NO: 16, 70, 150	hsa-miR-455-3p, hsa-miR-1250, hsa-miR-1254	81.6 %	77.2 %	86.0 %
816	SEQ ID NO: 135, 71, 243	hsa-miR-7-1*, hsa-miR-30e, hsa-miR-151-5p	81.6 %	80.4 %	82.8 %
817	SEQ ID NO: 251, 27, 252	hsa-miR-182, hsa-miR-423-5p, hsa-miR-497*	81.6 %	96.8 %	66.4 %

EP 2 865 765 A1

818	SEQ ID NO: 70, 252, 52	hsa-miR-1250, hsa-miR-497*, hsa-miR-802	81.5 %	90.0 %	73.0 %
819	SEQ ID NO: 174, 244, 135	hsa-miR-636, hsa-miR-874, hsa-miR-7-1*	81.4 %	71.2 %	91.6 %
820	SEQ ID NO: 243, 22, 135	hsa-miR-151-5p, hsa-miR-20b*, hsa-miR-7-1*	81.4 %	70.0 %	92.8 %
821	SEQ ID NO: 156, 243, 22	hsa-miR-217, hsa-miR-151-5p, hsa-miR-20b*	81.4 %	72.8 %	90.0 %
822	SEQ ID NO: 246, 59, 181	hsa-miR-20a, hsa-miR-1301, hsa-miR-145	81.3 %	84.6 %	78.0 %
823	SEQ ID NO: 71, 24, 244	hsa-miR-30e, hsa-miR-330-3p, hsa-miR-874	81.3 %	75.8 %	86.8 %
824	SEQ ID NO: 244, 135, 85	hsa-miR-874, hsa-miR-7-1*, hsa-miR-140-5p	81.2 %	69.6 %	92.8 %
825	SEQ ID NO: 27, 116, 62	hsa-miR-423-5p, hsa-miR-339-3p, hsa-miR-1281	81.2 %	86.8 %	75.6 %
826	SEQ ID NO: 251, 116, 252	hsa-miR-182, hsa-miR-339-3p, hsa-miR-497*	81.2 %	83.0 %	79.4 %
827	SEQ ID NO: 22, 32, 232	hsa-miR-20b*, hsa-miR-380*, hsa-miR-624	81.1 %	85.2 %	77.0 %
828	SEQ ID NO: 16, 32, 273	hsa-miR-455-3p, hsa-miR-380*, hsa-miR-194*	81.1 %	81.2 %	81.0 %
829	SEQ ID NO: 174, 135, 71	hsa-miR-636, hsa-miR-7-1*, hsa-miR-30e	81.0 %	75.8 %	86.2 %
830	SEQ ID NO: 27, 116, 252	hsa-miR-423-5p, hsa-miR-339-3p, hsa-miR-497*	81.0 %	87.4 %	74.6 %
831	SEQ ID NO: 70, 265, 150	hsa-miR-1250, hsa-miR-129-5p, hsa-miR-1254	81.0 %	83.8 %	78.2 %
832	SEQ ID NO: 156, 243, 135	hsa-miR-217, hsa-miR-151-5p, hsa-miR-7-1*	81.0 %	71.2 %	90.8 %
833	SEQ ID NO: 16, 70, 259	hsa-miR-455-3p, hsa-miR-1250, hsa-miR-631	80.9 %	75.0 %	86.8 %
834	SEQ ID NO: 156, 22, 135	hsa-miR-217, hsa-miR-20b*, hsa-miR-7-1*	80.9 %	70.4 %	91.4 %
835	SEQ ID NO: 24, 242, 259	hsa-miR-330-3p, hsa-let-7i, hsa-miR-631	80.8 %	73.4 %	88.2 %
836	SEQ ID NO: 71, 24, 167	hsa-miR-30e, hsa-miR-330-3p, hsa-miR-627	80.7 %	75.4 %	86.0 %
837	SEQ ID NO: 135, 31, 32	hsa-miR-7-1*, hsa-miR-139-5p, hsa-miR-380*	80.7 %	80.6 %	80.8 %
838	SEQ ID NO: 71, 242, 244	hsa-miR-30e, hsa-let-7i, hsa-miR-874	80.6 %	74.2 %	87.0 %
839	SEQ ID NO: 35, 167, 243	hsa-miR-188-3p, hsa-miR-627, hsa-miR-151-5p	80.6 %	80.8 %	80.4 %
840	SEQ ID NO: 156, 266, 231	hsa-miR-217, hsa-miR-615-5p, hsa-miR-93	80.6 %	83.4 %	77.8 %
841	SEQ ID NO: 231, 269, 32	hsa-miR-93, hsa-miR-105, hsa-miR-380*	80.6 %	77.0 %	84.2 %
842	SEQ ID NO: 31, 123, 22	hsa-miR-139-5p, hsa-miR-146b-3p, hsa-miR-20b*	80.4 %	85.6 %	75.2 %
843	SEQ ID NO: 246, 247, 181	hsa-miR-20a, hsa-miR-148a, hsa-miR-145	80.4 %	86.6 %	74.2 %
844	SEQ ID NO: 245, 155, 247	hsa-miR-106a, hsa-miR-484, hsa-miR-148a	80.4 %	89.4 %	71.4 %
845	SEQ ID NO: 66, 155, 169	hsa-miR-1295, hsa-miR-484, hsa-miR-324-3p	80.4 %	79.8 %	81.0 %
846	SEQ ID NO: 95, 150, 156	hsa-miR-135b*, hsa-miR-1254, hsa-miR-217	80.4 %	85.0 %	75.8 %
847	SEQ ID NO: 31, 16, 32	hsa-miR-139-5p, hsa-miR-455-3p, hsa-miR-380*	80.4 %	80.4 %	80.4 %
848	SEQ ID NO: 22, 232, 135	hsa-miR-20b*, hsa-miR-624, hsa-miR-7-1*	80.3 %	77.2 %	83.4 %
849	SEQ ID NO: 59, 181, 248	hsa-miR-1301, hsa-miR-145, hsa-let-7b	80.2 %	95.0 %	65.4 %

EP 2 865 765 A1

			%	%	%
850	SEQ ID NO: 16, 32, 23	hsa-miR-455-3p, hsa-miR-380*, hsa-miR-491-3p	80.2 %	75.8 %	84.6 %
851	SEQ ID NO: 244, 135, 71	hsa-miR-874, hsa-miR-7-1*, hsa-miR-30e	80.1 %	75.0 %	85.2 %
852	SEQ ID NO: 169, 246, 181	hsa-miR-324-3p, hsa-miR-20a, hsa-miR-145	80.1 %	79.6 %	80.6 %
853	SEQ ID NO: 150, 265, 266	hsa-miR-1254, hsa-miR-129-5p, hsa-miR-615-5p	80.1 %	85.2 %	75.0 %
854	SEQ ID NO: 15, 123, 244	hsa-miR-892b, hsa-miR-146b-3p, hsa-miR-874	80.0 %	90.0 %	70.0 %
855	SEQ ID NO: 259, 125, 66	hsa-miR-631, hsa-miR-1285, hsa-miR-1295	80.0 %	84.6 %	75.4 %
856	SEQ ID NO: 24, 242, 244	hsa-miR-330-3p, hsa-let-7i, hsa-miR-874	79.9 %	75.0 %	84.8 %
857	SEQ ID NO: 123, 95, 150	hsa-miR-146b-3p, hsa-miR-135b*, hsa-miR-1254	79.9 %	87.4 %	72.4 %
858	SEQ ID NO: 32, 232, 135	hsa-miR-380*, hsa-miR-624, hsa-miR-7-1*	79.7 %	85.2 %	74.2 %
859	SEQ ID NO: 156, 231, 22	hsa-miR-217, hsa-miR-93, hsa-miR-20b*	79.7 %	75.8 %	83.6 %
860	SEQ ID NO: 155, 169, 247	hsa-miR-484, hsa-miR-324-3p, hsa-miR-148a	79.6 %	85.0 %	74.2 %
861	SEQ ID NO: 244, 125, 155	hsa-miR-874, hsa-miR-1285, hsa-miR-484	79.5 %	79.0 %	80.0 %
862	SEQ ID NO: 156, 24, 231	hsa-miR-217, hsa-miR-330-3p, hsa-miR-93	79.5 %	79.8 %	79.2 %
863	SEQ ID NO: 150, 123, 95	hsa-miR-1254, hsa-miR-146b-3p, hsa-miR-135b*	79.4 %	87.2 %	71.6 %
864	SEQ ID NO: 32, 23, 24	hsa-miR-380*, hsa-miR-491-3p, hsa-miR-330-3p	79.3 %	73.8 %	84.8 %
865	SEQ ID NO: 22, 174, 244	hsa-miR-20b*, hsa-miR-636, hsa-miR-874	79.2 %	75.2 %	83.2 %
866	SEQ ID NO: 244, 231, 155	hsa-miR-874, hsa-miR-93, hsa-miR-484	79.2 %	72.8 %	85.6 %
867	SEQ ID NO: 24, 242, 125	hsa-miR-330-3p, hsa-let-7i, hsa-miR-1285	79.2 %	72.6 %	85.8 %
868	SEQ ID NO: 250, 217, 116	hsa-miR-374a, hsa-miR-148b, hsa-miR-339-3p	79.2 %	76.6 %	81.8 %
869	SEQ ID NO: 244, 125, 245	hsa-miR-874, hsa-miR-1285, hsa-miR-106a	79.1 %	77.6 %	80.6 %
870	SEQ ID NO: 59, 181, 249	hsa-miR-1301, hsa-miR-145, hsa-miR-33b*	79.1 %	93.2 %	65.0 %
871	SEQ ID NO: 266, 265, 150	hsa-miR-615-5p, hsa-miR-129-5p, hsa-miR-1254	79.1 %	83.8 %	74.4 %
872	SEQ ID NO: 22, 135, 31	hsa-miR-20b*, hsa-miR-7-1*, hsa-miR-139-5p	79.1 %	71.8 %	86.4 %
873	SEQ ID NO: 135, 254, 71	hsa-miR-7-1*, hsa-miR-323-3p, hsa-miR-30e	79.0 %	77.0 %	81.0 %
874	SEQ ID NO: 24, 167, 242	hsa-miR-330-3p, hsa-miR-627, hsa-let-7i	79.0 %	71.2 %	86.8 %
875	SEQ ID NO: 31, 16, 273	hsa-miR-139-5p, hsa-miR-455-3p, hsa-miR-194*	79.0 %	79.8 %	78.2 %
876	SEQ ID NO: 155, 247, 59	hsa-miR-484, hsa-miR-148a, hsa-miR-1301	78.9 %	88.0 %	69.8 %
877	SEQ ID NO: 265, 150, 15	hsa-miR-129-5p, hsa-miR-1254, hsa-miR-892b	78.9 %	83.8 %	74.0 %
878	SEQ ID NO: 150, 265, 156	hsa-miR-1254, hsa-miR-129-5p, hsa-miR-217	78.8 %	86.8 %	70.8 %
879	SEQ ID NO: 156, 266, 22	hsa-miR-217, hsa-miR-615-5p, hsa-miR-20b*	78.8 %	76.2 %	81.4 %
880	SEQ ID NO: 265, 24, 231	hsa-miR-129-5p, hsa-miR-330-3p, hsa-miR-93	78.8 %	75.2 %	82.4 %

EP 2 865 765 A1

881	SEQ ID NO: 16, 252, 23	hsa-miR-455-3p, hsa-miR-497*, hsa-miR-491-3p	78.6 %	84.6 %	72.6 %
882	SEQ ID NO: 125, 231, 66	hsa-miR-1285, hsa-miR-93, hsa-miR-1295	78.5 %	80.4 %	76.6 %
883	SEQ ID NO: 95, 150, 266	hsa-miR-135b*, hsa-miR-1254, hsa-miR-615-5p	78.5 %	79.6 %	77.4 %
884	SEQ ID NO: 125, 66, 245	hsa-miR-1285, hsa-miR-1295, hsa-miR-106a	78.2 %	83.6 %	72.8 %
885	SEQ ID NO: 174, 255, 35	hsa-miR-636, hsa-miR-193a-3p, hsa-miR-188-3p	78.2 %	86.6 %	69.8 %
886	SEQ ID NO: 273, 252, 23	hsa-miR-194*, hsa-miR-497*, hsa-miR-491-3p	78.2 %	85.6 %	70.8 %
887	SEQ ID NO: 19, 31, 32	hsa-miR-767-5p, hsa-miR-139-5p, hsa-miR-380*	78.2 %	76.6 %	79.8 %
888	SEQ ID NO: 248, 12, 250	hsa-let-7b, hsa-miR-128, hsa-miR-374a	78.1 %	75.6 %	80.6 %
889	SEQ ID NO: 125, 66, 155	hsa-miR-1285, hsa-miR-1295, hsa-miR-484	78.0 %	74.0 %	82.0 %
890	SEQ ID NO: 247, 59, 181	hsa-miR-148a, hsa-miR-1301, hsa-miR-145	77.9 %	77.6 %	78.2 %
891	SEQ ID NO: 245, 246, 247	hsa-miR-106a, hsa-miR-20a, hsa-miR-148a	77.9 %	86.6 %	69.2 %
892	SEQ ID NO: 250, 251, 217	hsa-miR-374a, hsa-miR-182, hsa-miR-148b	77.8 %	78.4 %	77.2 %
893	SEQ ID NO: 32, 259, 95	hsa-miR-380*, hsa-miR-631, hsa-miR-135b*	77.7 %	78.4 %	77.0 %
894	SEQ ID NO: 217, 116, 252	hsa-miR-148b, hsa-miR-339-3p, hsa-miR-497*	77.7 %	78.8 %	76.6 %
895	SEQ ID NO: 231, 66, 155	hsa-miR-93, hsa-miR-1295, hsa-miR-484	77.7 %	73.4 %	82.0 %
896	SEQ ID NO: 181, 12, 249	hsa-miR-145, hsa-miR-128, hsa-miR-33b*	77.6 %	71.8 %	83.4 %
897	SEQ ID NO: 244, 125, 66	hsa-miR-874, hsa-miR-1285, hsa-miR-1295	77.5 %	75.4 %	79.6 %
898	SEQ ID NO: 150, 135, 71	hsa-miR-1254, hsa-miR-7-1*, hsa-miR-30e	77.5 %	66.4 %	88.6 %
899	SEQ ID NO: 252, 23, 24	hsa-miR-497*, hsa-miR-491-3p, hsa-miR-330-3p	77.5 %	80.4 %	74.6 %
900	SEQ ID NO: 135, 242, 243	hsa-miR-7-1*, hsa-let-7i, hsa-miR-151-5p	77.4 %	84.8 %	70.0 %
901	SEQ ID NO: 265, 156, 266	hsa-miR-129-5p, hsa-miR-217, hsa-miR-615-5p	77.4 %	88.4 %	66.4 %
902	SEQ ID NO: 259, 231, 66	hsa-miR-631, hsa-miR-93, hsa-miR-1295	77.1 %	78.4 %	75.8 %
903	SEQ ID NO: 95, 265, 156	hsa-miR-135b*, hsa-miR-129-5p, hsa-miR-217	77.1 %	84.0 %	70.2 %
904	SEQ ID NO: 231, 155, 169	hsa-miR-93, hsa-miR-484, hsa-miR-324-3p	77.0 %	71.4 %	82.6 %
905	SEQ ID NO: 269, 32, 71	hsa-miR-105, hsa-miR-380*, hsa-miR-30e	77.0 %	80.0 %	74.0 %
906	SEQ ID NO: 24, 167, 259	hsa-miR-330-3p, hsa-miR-627, hsa-miR-631	76.9 %	77.4 %	76.4 %
907	SEQ ID NO: 66, 169, 246	hsa-miR-1295, hsa-miR-324-3p, hsa-miR-20a	76.8 %	80.6 %	73.0 %
908	SEQ ID NO: 95, 156, 266	hsa-miR-135b*, hsa-miR-217, hsa-miR-615-5p	76.7 %	73.6 %	79.8 %
909	SEQ ID NO: 125, 231, 155	hsa-miR-1285, hsa-miR-93, hsa-miR-484	76.6 %	68.4 %	84.8 %
910	SEQ ID NO: 244, 231, 245	hsa-miR-874, hsa-miR-93, hsa-miR-106a	76.6 %	73.6 %	79.6 %
911	SEQ ID NO: 247, 181, 12	hsa-miR-148a, hsa-miR-145, hsa-miR-128	76.6 %	83.4 %	69.8 %
912	SEQ ID NO: 125, 231,	hsa-miR-1285, hsa-miR-93, hsa-miR-324-	76.6	68.2	85.0

EP 2 865 765 A1

	169	3p	%	%	%
913	SEQ ID NO: 242, 125, 231	hsa-let-7i, hsa-miR-1285, hsa-miR-93	76.6 %	70.0 %	83.2 %
914	SEQ ID NO: 251, 27, 217	hsa-miR-182, hsa-miR-423-5p, hsa-miR-148b	76.5 %	71.0 %	82.0 %
915	SEQ ID NO: 150, 156, 266	hsa-miR-1254, hsa-miR-217, hsa-miR-615-5p	76.5 %	78.8 %	74.2 %
916	SEQ ID NO: 16, 273, 252	hsa-miR-455-3p, hsa-miR-194*, hsa-miR-497*	76.4 %	80.8 %	72.0 %
917	SEQ ID NO: 169, 247, 181	hsa-miR-324-3p, hsa-miR-148a, hsa-miR-145	76.3 %	72.8 %	79.8 %
918	SEQ ID NO: 155, 246, 247	hsa-miR-484, hsa-miR-20a, hsa-miR-148a	76.1 %	84.6 %	67.6 %
919	SEQ ID NO: 169, 59, 181	hsa-miR-324-3p, hsa-miR-1301, hsa-miR-145	76.1 %	85.2 %	67.0 %
920	SEQ ID NO: 19, 31, 273	hsa-miR-767-5p, hsa-miR-139-5p, hsa-miR-194*	76.1 %	81.8 %	70.4 %
921	SEQ ID NO: 155, 169, 59	hsa-miR-484, hsa-miR-324-3p, hsa-miR-1301	76.0 %	76.6 %	75.4 %
922	SEQ ID NO: 244, 231, 66	hsa-miR-874, hsa-miR-93, hsa-miR-1295	76.0 %	77.6 %	74.4 %
923	SEQ ID NO: 59, 248, 249	hsa-miR-1301, hsa-let-7b, hsa-miR-33b*	75.9 %	83.0 %	68.8 %
924	SEQ ID NO: 41, 251, 217	hsa-miR-654-5p, hsa-miR-182, hsa-miR-148b	75.7 %	75.4 %	76.0 %
925	SEQ ID NO: 95, 150, 265	hsa-miR-135b*, hsa-miR-1254, hsa-miR-129-5p	75.7 %	81.0 %	70.4 %
926	SEQ ID NO: 95, 156, 243	hsa-miR-135b*, hsa-miR-217, hsa-miR-151-5p	75.7 %	68.0 %	83.4 %
927	SEQ ID NO: 255, 35, 167	hsa-miR-193a-3p, hsa-miR-188-3p, hsa-miR-627	75.6 %	90.0 %	61.2 %
928	SEQ ID NO: 231, 66, 245	hsa-miR-93, hsa-miR-1295, hsa-miR-106a	75.5 %	75.0 %	76.0 %
929	SEQ ID NO: 167, 259, 244	hsa-miR-627, hsa-miR-631, hsa-miR-874	75.5 %	79.8 %	71.2 %
930	SEQ ID NO: 125, 155, 169	hsa-miR-1285, hsa-miR-484, hsa-miR-324-3p	75.4 %	69.6 %	81.2 %
931	SEQ ID NO: 16, 273, 23	hsa-miR-455-3p, hsa-miR-194*, hsa-miR-491-3p	75.4 %	74.4 %	76.4 %
932	SEQ ID NO: 59, 12, 249	hsa-miR-1301, hsa-miR-128, hsa-miR-33b*	75.3 %	83.8 %	66.8 %
933	SEQ ID NO: 66, 245, 246	hsa-miR-1295, hsa-miR-106a, hsa-miR-20a	75.3 %	80.4 %	70.2 %
934	SEQ ID NO: 41, 250, 27	hsa-miR-654-5p, hsa-miR-374a, hsa-miR-423-5p	75.1 %	68.4 %	81.8 %
935	SEQ ID NO: 66, 155, 246	hsa-miR-1295, hsa-miR-484, hsa-miR-20a	74.9 %	79.6 %	70.2 %
936	SEQ ID NO: 244, 66, 245	hsa-miR-874, hsa-miR-1295, hsa-miR-106a	74.9 %	76.0 %	73.8 %
937	SEQ ID NO: 265, 156, 231	hsa-miR-129-5p, hsa-miR-217, hsa-miR-93	74.9 %	77.8 %	72.0 %
938	SEQ ID NO: 32, 135, 71	hsa-miR-380*, hsa-miR-7-1*, hsa-miR-30e	74.8 %	67.4 %	82.2 %
939	SEQ ID NO: 231, 66, 169	hsa-miR-93, hsa-miR-1295, hsa-miR-324-3p	74.7 %	76.4 %	73.0 %
940	SEQ ID NO: 259, 244, 66	hsa-miR-631, hsa-miR-874, hsa-miR-1295	74.5 %	79.6 %	69.4 %
941	SEQ ID NO: 251, 27, 116	hsa-miR-182, hsa-miR-423-5p, hsa-miR-339-3p	74.4 %	69.8 %	79.0 %
942	SEQ ID NO: 181, 12, 41	hsa-miR-145, hsa-miR-128, hsa-miR-654-5p	74.4 %	67.2 %	81.6 %
943	SEQ ID NO: 150, 95, 31	hsa-miR-1254, hsa-miR-135b*, hsa-miR-139-5p	74.0 %	77.8 %	70.2 %

EP 2 865 765 A1

944	SEQ ID NO: 27, 217, 116	hsa-miR-423-5p, hsa-miR-148b, hsa-miR-339-3p	74.0 %	78.2 %	69.8 %
945	SEQ ID NO: 247, 59, 248	hsa-miR-148a, hsa-miR-1301, hsa-let-7b	74.0 %	84.2 %	63.8 %
946	SEQ ID NO: 244, 245, 155	hsa-miR-874, hsa-miR-106a, hsa-miR-484	74.0 %	64.6 %	83.4 %
947	SEQ ID NO: 35, 24, 167	hsa-miR-188-3p, hsa-miR-330-3p, hsa-miR-627	73.9 %	70.4 %	77.4 %
948	SEQ ID NO: 248, 249, 250	hsa-let-7b, hsa-miR-33b*, hsa-miR-374a	73.7 %	69.8 %	77.6 %
949	SEQ ID NO: 125, 231, 245	hsa-miR-1285, hsa-miR-93, hsa-miR-106a	73.6 %	71.6 %	75.6 %
950	SEQ ID NO: 248, 12, 41	hsa-let-7b, hsa-miR-128, hsa-miR-654-5p	73.6 %	62.0 %	85.2 %
951	SEQ ID NO: 248, 249, 41	hsa-let-7b, hsa-miR-33b*, hsa-miR-654-5p	73.3 %	70.4 %	76.2 %
952	SEQ ID NO: 95, 265, 266	hsa-miR-135b*, hsa-miR-129-5p, hsa-miR-615-5p	73.3 %	72.0 %	74.6 %
953	SEQ ID NO: 156, 269, 243	hsa-miR-217, hsa-miR-105, hsa-miR-151-5p	73.2 %	74.6 %	71.8 %
954	SEQ ID NO: 41, 250, 251	hsa-miR-654-5p, hsa-miR-374a, hsa-miR-182	73.1 %	82.8 %	63.4 %
955	SEQ ID NO: 41, 251, 27	hsa-miR-654-5p, hsa-miR-182, hsa-miR-423-5p	73.0 %	77.4 %	68.6 %
956	SEQ ID NO: 248, 12, 249	hsa-let-7b, hsa-miR-128, hsa-miR-33b*	72.8 %	62.6 %	83.0 %
957	SEQ ID NO: 19, 16, 273	hsa-miR-767-5p, hsa-miR-455-3p, hsa-miR-194*	72.7 %	77.8 %	67.6 %
958	SEQ ID NO: 12, 249, 41	hsa-miR-128, hsa-miR-33b*, hsa-miR-654-5p	72.6 %	68.6 %	76.6 %
959	SEQ ID NO: 247, 59, 12	hsa-miR-148a, hsa-miR-1301, hsa-miR-128	72.4 %	86.8 %	58.0 %
960	SEQ ID NO: 66, 245, 169	hsa-miR-1295, hsa-miR-106a, hsa-miR-324-3p	72.3 %	78.2 %	66.4 %
961	SEQ ID NO: 231, 169, 246	hsa-miR-93, hsa-miR-324-3p, hsa-miR-20a	72.1 %	65.0 %	79.2 %
962	SEQ ID NO: 249, 41, 27	hsa-miR-33b*, hsa-miR-654-5p, hsa-miR-423-5p	71.9 %	64.0 %	79.8 %
963	SEQ ID NO: 155, 169, 246	hsa-miR-484, hsa-miR-324-3p, hsa-miR-20a	71.6 %	64.4 %	78.8 %
964	SEQ ID NO: 231, 155, 246	hsa-miR-93, hsa-miR-484, hsa-miR-20a	71.4 %	72.2 %	70.6 %
965	SEQ ID NO: 248, 41, 250	hsa-let-7b, hsa-miR-654-5p, hsa-miR-374a	71.4 %	70.6 %	72.2 %
966	SEQ ID NO: 231, 245, 155	hsa-miR-93, hsa-miR-106a, hsa-miR-484	71.3 %	72.2 %	70.4 %
967	SEQ ID NO: 135, 71, 242	hsa-miR-7-1*, hsa-miR-30e, hsa-let-7i	71.3 %	69.2 %	73.4 %
968	SEQ ID NO: 273, 23, 24	hsa-miR-194*, hsa-miR-491-3p, hsa-miR-330-3p	71.2 %	70.6 %	71.8 %
969	SEQ ID NO: 181, 248, 41	hsa-miR-145, hsa-let-7b, hsa-miR-654-5p	71.0 %	78.8 %	63.2 %
970	SEQ ID NO: 245, 155, 169	hsa-miR-106a, hsa-miR-484, hsa-miR-324-3p	70.9 %	68.4 %	73.4 %
971	SEQ ID NO: 251, 217, 116	hsa-miR-182, hsa-miR-148b, hsa-miR-339-3p	70.9 %	60.0 %	81.8 %
972	SEQ ID NO: 12, 249, 251	hsa-miR-128, hsa-miR-33b*, hsa-miR-182	70.9 %	61.6 %	80.2 %
973	SEQ ID NO: 246, 247, 59	hsa-miR-20a, hsa-miR-148a, hsa-miR-1301	70.8 %	86.6 %	55.0 %
974	SEQ ID NO: 231, 245, 169	hsa-miR-93, hsa-miR-106a, hsa-miR-324-3p	70.6 %	67.2 %	74.0 %
975	SEQ ID NO: 249, 41, 251	hsa-miR-33b*, hsa-miR-654-5p, hsa-miR-	70.6 %	77.0 %	64.2 %

EP 2 865 765 A1

		182	%	%	%
976	SEQ ID NO: 245, 169, 246	hsa-miR-106a, hsa-miR-324-3p, hsa-miR-20a	70.6 %	70.8 %	70.4 %
977	SEQ ID NO: 247, 181, 248	hsa-miR-148a, hsa-miR-145, hsa-let-7b	70.4 %	64.6 %	76.2 %
978	SEQ ID NO: 125, 245, 169	hsa-miR-1285, hsa-miR-106a, hsa-miR-324-3p	70.4 %	67.0 %	73.8 %
979	SEQ ID NO: 247, 248, 12	hsa-miR-148a, hsa-let-7b, hsa-miR-128	70.3 %	73.2 %	67.4 %
980	SEQ ID NO: 12, 250, 251	hsa-miR-128, hsa-miR-374a, hsa-miR-182	70.1 %	74.4 %	65.8 %
981	SEQ ID NO: 12, 249, 250	hsa-miR-128, hsa-miR-33b*, hsa-miR-374a	70.0 %	71.4 %	68.6 %
982	SEQ ID NO: 246, 247, 248	hsa-miR-20a, hsa-miR-148a, hsa-let-7b	69.6 %	73.0 %	66.2 %
983	SEQ ID NO: 181, 248, 249	hsa-miR-145, hsa-let-7b, hsa-miR-33b*	69.3 %	78.6 %	60.0 %
984	SEQ ID NO: 249, 250, 27	hsa-miR-33b*, hsa-miR-374a, hsa-miR-423-5p	69.3 %	71.8 %	66.8 %
985	SEQ ID NO: 59, 248, 12	hsa-miR-1301, hsa-let-7b, hsa-miR-128	69.1 %	80.4 %	57.8 %
986	SEQ ID NO: 169, 246, 59	hsa-miR-324-3p, hsa-miR-20a, hsa-miR-1301	68.9 %	73.4 %	64.4 %
987	SEQ ID NO: 125, 245, 155	hsa-miR-1285, hsa-miR-106a, hsa-miR-484	68.7 %	68.4 %	69.0 %
988	SEQ ID NO: 231, 245, 246	hsa-miR-93, hsa-miR-106a, hsa-miR-20a	67.6 %	78.8 %	56.4 %
989	SEQ ID NO: 169, 246, 247	hsa-miR-324-3p, hsa-miR-20a, hsa-miR-148a	67.5 %	70.6 %	64.4 %
990	SEQ ID NO: 245, 169, 247	hsa-miR-106a, hsa-miR-324-3p, hsa-miR-148a	67.5 %	73.2 %	61.8 %
991	SEQ ID NO: 181, 249, 41	hsa-miR-145, hsa-miR-33b*, hsa-miR-654-5p	66.8 %	77.6 %	56.0 %
992	SEQ ID NO: 250, 27, 116	hsa-miR-374a, hsa-miR-423-5p, hsa-miR-339-3p	66.7 %	72.2 %	61.2 %
993	SEQ ID NO: 155, 246, 59	hsa-miR-484, hsa-miR-20a, hsa-miR-1301	66.5 %	64.0 %	69.0 %
994	SEQ ID NO: 249, 251, 27	hsa-miR-33b*, hsa-miR-182, hsa-miR-423-5p	65.9 %	65.6 %	66.2 %
995	SEQ ID NO: 12, 41, 251	hsa-miR-128, hsa-miR-654-5p, hsa-miR-182	65.7 %	64.8 %	66.6 %
996	SEQ ID NO: 12, 41, 250	hsa-miR-128, hsa-miR-654-5p, hsa-miR-374a	65.5 %	60.0 %	71.0 %
997	SEQ ID NO: 246, 59, 248	hsa-miR-20a, hsa-miR-1301, hsa-let-7b	65.3 %	72.6 %	58.0 %
998	SEQ ID NO: 169, 247, 59	hsa-miR-324-3p, hsa-miR-148a, hsa-miR-1301	64.8 %	65.0 %	64.6 %
999	SEQ ID NO: 181, 248, 12	hsa-miR-145, hsa-let-7b, hsa-miR-128	62.9 %	63.4 %	62.4 %
1000	SEQ ID NO: 249, 41, 250	hsa-miR-33b*, hsa-miR-654-5p, hsa-miR-374a	62.4 %	55.8 %	69.0 %
1001	SEQ ID NO: 250, 251, 116	hsa-miR-374a, hsa-miR-182, hsa-miR-339-3p	62.4 %	63.4 %	61.4 %
1002	SEQ ID NO: 245, 155, 246	hsa-miR-106a, hsa-miR-484, hsa-miR-20a	61.0 %	59.4 %	62.6 %
1003	SEQ ID NO: 249, 250, 251	hsa-miR-33b*, hsa-miR-374a, hsa-miR-182	60.5 %	70.6 %	50.4 %
1004	SEQ ID NO: 250, 251, 27	hsa-miR-374a, hsa-miR-182, hsa-miR-423-5p	60.2 %	63.8 %	56.6 %

EP 2 865 765 A1

1005	SEQ ID NO: 162, 157, 234, 184, 68, 16, 70, 252, 52, 15, 243, 62, 123, 95, 150, 22, 32, 259, 253, 31	hsa-miR-142-5p, hsa-miR-566, hsa-miR-498, hsa-miR-492, hsa-miR-23b*, hsa-miR-455-3p, hsa-miR-1250, hsa-miR-497*, hsa-miR-802, hsa-miR-892b, hsa-miR-151-5p, hsa-miR-1281, hsa-miR-146b-3p, hsa-miR-135b*, hsa-miR-1254, hsa-miR-20b*, hsa-miR-380*, hsa-miR-631, hsa-miR-345, hsa-miR-139-5p	93%	96%	90%
------	---	--	-----	-----	-----

Figure 29

SEQ ID NO:	miRNA	median g1	median g2	qmedian	logqmedian	ttest_raw p	ttest_adj p	AUC	limma_raw p	limma_adj p
162	hsa-miR-142-5p	644	1413	0.46	-0.79	4.00E-08	2.79E-05	0.063	2.35E-06	2.34E-04
257	hsa-miR-663b	119	45	2.65	0.98	1.86E-03	2.35E-02	0.935	3.34E-05	1.79E-03
234	hsa-miR-498	1	41	0.02	-3.70	1.15E-06	4.02E-04	0.065	7.78E-11	5.42E-08
157	hsa-miR-566	82	13	6.11	1.81	5.28E-05	2.47E-03	0.903	1.07E-06	1.87E-04
184	hsa-miR-492	79	12	6.59	1.89	9.22E-06	1.37E-03	0.888	1.62E-06	2.16E-04
68	hsa-miR-23b*	1	68	0.01	-4.23	2.05E-05	1.78E-03	0.100	1.66E-07	5.77E-05
16	hsa-miR-455-3p	200	52	3.84	1.35	2.31E-05	1.79E-03	0.878	2.28E-04	5.95E-03
70	hsa-miR-1250	5	97	0.05	-2.93	3.00E-05	2.09E-03	0.115	4.26E-06	3.30E-04
252	hsa-miR-497*	141	56	2.49	0.91	9.83E-06	1.37E-03	0.876	2.88E-04	6.91E-03
137	hsa-miR-920	1	71	0.02	-3.88	2.44E-03	2.80E-02	0.123	1.86E-06	2.16E-04
52	hsa-miR-802	82	1	82.20	4.41	1.79E-05	1.78E-03	0.875	7.22E-07	1.68E-04
15	hsa-miR-892b	9	89	0.10	-2.34	7.88E-05	2.96E-03	0.129	5.12E-05	2.38E-03
62	hsa-miR-1281	66	210	0.31	-1.16	9.64E-06	1.37E-03	0.129	1.48E-02	6.88E-02
243	hsa-miR-151-5p	9353	5101	1.83	0.61	1.59E-05	1.78E-03	0.875	1.01E-04	3.70E-03
95	hsa-miR-135b*	23	82	0.28	-1.27	5.01E-05	2.47E-03	0.130	7.09E-05	2.91E-03
123	hsa-miR-146b-3p	83	28	2.98	1.09	8.06E-05	2.96E-03	0.873	5.01E-05	2.38E-03
150	hsa-miR-1254	162	78	2.07	0.73	5.67E-05	2.47E-03	0.868	2.81E-05	1.63E-03
265	hsa-miR-129-5p	1	42	0.02	-3.74	1.00E-03	1.55E-02	0.161	1.61E-05	1.02E-03
266	hsa-miR-615-5p	1	68	0.02	-4.03	1.13E-03	1.63E-02	0.163	1.19E-05	8.26E-04
156	hsa-miR-217	127	27	4.63	1.53	1.58E-03	2.08E-02	0.868	6.71E-05	2.91E-03
24	hsa-miR-	432	156	2.76	1.02	4.85E-04	1.03E-02	0.864	3.80E-04	8.02E-03

EP 2 865 765 A1

	330-3p									
231	hsa-miR-93	4593	5727	0.80	-0.22	1.15E-03	1.63E-02	0.163	2.27E-03	2.14E-02
22	hsa-miR-20b*	67	17	3.95	1.37	1.17E-04	4.06E-03	0.860	1.32E-04	4.26E-03
269	hsa-miR-105	12	47	0.25	-1.37	1.39E-03	1.86E-02	0.170	8.34E-05	3.23E-03
32	hsa-miR-380*	65	30	2.19	0.78	3.42E-05	2.17E-03	0.854	2.30E-04	5.95E-03
232	hsa-miR-624	21	72	0.29	-1.23	5.18E-04	1.03E-02	0.170	7.98E-03	4.63E-02
135	hsa-miR-7-1*	462	223	2.07	0.73	1.58E-04	4.78E-03	0.845	1.35E-04	4.26E-03
71	hsa-miR-30e	239	486	0.49	-0.71	2.87E-04	8.00E-03	0.183	3.64E-03	2.85E-02
259	hsa-miR-631	157	95	1.64	0.49	5.63E-05	2.47E-03	0.845	3.03E-03	2.47E-02
85	hsa-miR-140-5p	1	78	0.01	-4.36	3.41E-04	8.81E-03	0.184	4.51E-04	8.49E-03
253	hsa-miR-345	198	91	2.17	0.78	5.25E-05	2.47E-03	0.843	5.61E-04	1.00E-02
261	hsa-miR-200b*	5	84	0.06	-2.82	4.77E-04	1.03E-02	0.186	4.24E-04	8.49E-03
19	hsa-miR-767-5p	156	48	3.23	1.17	5.72E-04	1.05E-02	0.839	1.50E-04	4.42E-03
267	hsa-miR-193b	33	81	0.41	-0.90	1.08E-03	1.63E-02	0.188	3.32E-03	2.65E-02
174	hsa-miR-636	168	84	2.01	0.70	1.28E-04	4.23E-03	0.839	3.74E-04	8.02E-03
148	hsa-miR-1304	32	67	0.48	-0.73	6.09E-03	4.37E-02	0.195	2.59E-03	2.27E-02
255	hsa-miR-193a-3p	166	75	2.21	0.79	3.31E-04	8.81E-03	0.835	7.00E-02	1.89E-01
256	hsa-miR-134	10	102	0.10	-2.31	8.90E-04	1.44E-02	0.198	1.43E-03	1.89E-02
31	hsa-miR-139-5p	122	38	3.25	1.18	7.17E-05	2.94E-03	0.833	1.60E-04	4.47E-03
263	hsa-miR-409-3p	3	63	0.05	-3.00	5.55E-04	1.05E-02	0.198	2.00E-03	2.08E-02
244	hsa-miR-874	230	145	1.58	0.46	1.52E-04	4.78E-03	0.833	1.74E-03	2.07E-02
260	hsa-miR-544	9	49	0.18	-1.71	4.36E-04	9.99E-03	0.198	2.92E-03	2.45E-02
29	hsa-miR-33a	103	35	2.91	1.07	4.44E-04	9.99E-03	0.830	1.86E-03	2.07E-02
273	hsa-miR-194*	1	70	0.01	-4.24	3.46E-03	3.18E-02	0.200	2.46E-04	6.13E-03
35	hsa-	137	51	2.71	1.00	3.83E-04	9.53E-03	0.824	6.62E-04	1.13E-02

EP 2 865 765 A1

	miR-188-3p									
268	hsa-miR-877*	18	81	0.23	-1.49	1.30E-03	1.78E-02	0.201	3.68E-03	2.85E-02
84	hsa-miR-1303	8	87	0.10	-2.35	4.10E-04	9.85E-03	0.206	7.85E-04	1.22E-02
125	hsa-miR-1285	303	191	1.59	0.46	6.91E-04	1.18E-02	0.815	1.07E-02	5.55E-02
262	hsa-miR-326	96	36	2.69	0.99	5.01E-04	1.03E-02	0.808	7.37E-04	1.20E-02
195	hsa-miR-142-3p	1	85	0.01	-4.44	1.11E-03	1.63E-02	0.210	7.05E-04	1.17E-02
264	hsa-miR-513a-5p	60	12	4.86	1.58	6.31E-04	1.13E-02	0.805	1.24E-03	1.70E-02
270	hsa-miR-296-3p	13	61	0.21	-1.56	2.52E-03	2.80E-02	0.210	9.41E-04	1.37E-02
55	hsa-miR-30e*	21	129	0.16	-1.83	6.81E-04	1.18E-02	0.213	1.58E-03	2.01E-02
169	hsa-miR-324-3p	927	598	1.55	0.44	2.56E-03	2.80E-02	0.805	4.03E-02	1.30E-01
254	hsa-miR-323-3p	103	12	8.22	2.11	2.81E-04	8.00E-03	0.803	3.34E-03	2.65E-02
216	hsa-miR-658	21	75	0.28	-1.28	1.74E-03	2.25E-02	0.214	7.77E-04	1.22E-02
276	hsa-miR-337-5p	48	19	2.58	0.95	5.02E-03	3.80E-02	0.799	5.32E-03	3.64E-02
279	hsa-miR-323-5p	42	95	0.44	-0.82	6.70E-03	4.62E-02	0.218	4.88E-03	3.50E-02
242	hsa-let-7i	478	970	0.49	-0.71	9.98E-04	1.55E-02	0.219	6.45E-03	4.08E-02
233	hsa-miR-433	90	18	5.12	1.63	4.23E-03	3.58E-02	0.794	1.70E-03	2.07E-02
167	hsa-miR-627	156	71	2.19	0.78	5.69E-04	1.05E-02	0.793	2.11E-03	2.10E-02
245	hsa-miR-106a	6564	8895	0.74	-0.30	2.02E-03	2.43E-02	0.219	1.57E-02	7.06E-02
215	hsa-miR-409-5p	85	31	2.76	1.01	3.08E-03	3.00E-02	0.790	4.71E-04	8.63E-03
250	hsa-miR-374a	283	502	0.56	-0.57	4.63E-03	3.67E-02	0.229	4.30E-02	1.37E-01
23	hsa-miR-491-3p	63	1	62.78	4.14	2.72E-03	2.83E-02	0.788	3.36E-04	7.55E-03
181	hsa-miR-145	233	334	0.70	-0.36	3.79E-03	3.38E-02	0.233	1.99E-02	8.48E-02
60	hsa-miR-	28	1	28.19	3.34	2.64E-03	2.83E-02	0.788	4.38E-04	8.49E-03

EP 2 865 765 A1

	1302									
205	hsa-miR-521	38	113	0.34	-1.09	4.45E-03	3.65E-02	0.235	2.98E-03	2.47E-02
129	hsa-miR-1537	37	2	17.33	2.85	1.17E-03	1.63E-02	0.788	8.44E-04	1.28E-02
246	hsa-miR-20a	2944	4318	0.68	-0.38	2.53E-03	2.80E-02	0.236	9.02E-03	4.99E-02
30	hsa-miR-508-5p	82	44	1.86	0.62	2.79E-03	2.86E-02	0.788	1.99E-03	2.08E-02
113	hsa-miR-34b*	23	68	0.33	-1.10	3.38E-03	3.14E-02	0.239	1.07E-03	1.53E-02
43	hsa-miR-145*	68	1	67.56	4.21	7.81E-04	1.30E-02	0.783	1.91E-03	2.08E-02
271	hsa-miR-27a*	2	53	0.04	-3.21	3.11E-03	3.00E-02	0.243	5.23E-03	3.62E-02
76	hsa-miR-942	6	77	0.08	-2.49	2.91E-03	2.94E-02	0.245	6.77E-03	4.10E-02
59	hsa-miR-1301	194	108	1.80	0.59	3.09E-03	3.00E-02	0.783	5.24E-03	3.62E-02
272	hsa-miR-99b*	17	58	0.29	-1.25	3.23E-03	3.04E-02	0.246	8.97E-03	4.99E-02
14	hsa-miR-541	82	16	5.06	1.62	6.07E-03	4.37E-02	0.780	5.89E-04	1.03E-02
258	hsa-miR-499-3p	105	34	3.12	1.14	2.69E-03	2.83E-02	0.780	5.60E-03	3.72E-02
275	hsa-miR-608	1	44	0.02	-3.78	4.50E-03	3.65E-02	0.250	4.15E-03	3.14E-02
126	hsa-miR-371-5p	43	1	42.90	3.76	2.30E-03	2.72E-02	0.779	4.45E-04	8.49E-03
134	hsa-miR-411*	39	84	0.46	-0.78	3.69E-03	3.34E-02	0.255	3.07E-02	1.11E-01
66	hsa-miR-1295	108	57	1.91	0.65	1.98E-03	2.43E-02	0.773	1.95E-03	2.08E-02
248	hsa-let-7b	621	1180	0.53	-0.64	3.88E-03	3.38E-02	0.256	5.50E-03	3.69E-02
86	hsa-miR-218-1*	63	28	2.24	0.81	1.93E-03	2.40E-02	0.771	1.86E-03	2.07E-02
278	hsa-miR-579	1	19	0.05	-2.94	6.56E-03	4.57E-02	0.273	7.41E-03	4.42E-02
141	hsa-miR-875-5p	16	67	0.24	-1.43	4.43E-03	3.65E-02	0.274	5.50E-02	1.61E-01
92	hsa-miR-30c-1*	28	5	5.65	1.73	6.19E-03	4.37E-02	0.770	2.18E-03	2.13E-02
41	hsa-miR-654-5p	194	102	1.90	0.64	4.62E-03	3.67E-02	0.768	4.39E-03	3.29E-02

EP 2 865 765 A1

12	hsa-miR-128	663	460	1.44	0.36	3.88E-03	3.38E-02	0.765	1.49E-02	6.88E-02
39	hsa-miR-216a	119	41	2.90	1.06	4.87E-03	3.77E-02	0.763	4.97E-03	3.50E-02
247	hsa-miR-148a	1524	1049	1.45	0.37	3.14E-03	3.00E-02	0.759	8.75E-03	4.96E-02
217	hsa-miR-148b	690	524	1.32	0.27	5.03E-03	3.80E-02	0.759	2.10E-02	8.66E-02
7	hsa-miR-1278	38	3	11.08	2.40	5.81E-03	4.26E-02	0.758	1.61E-03	2.01E-02
274	hsa-miR-653	77	11	7.14	1.97	4.03E-03	3.47E-02	0.758	4.80E-03	3.49E-02
155	hsa-miR-484	8679	6342	1.37	0.31	2.57E-03	2.80E-02	0.753	1.86E-02	8.13E-02
116	hsa-miR-339-3p	338	223	1.51	0.41	5.35E-03	3.97E-02	0.751	6.65E-03	4.10E-02
277	hsa-miR-1207-3p	56	2	32.08	3.47	6.20E-03	4.37E-02	0.749	5.94E-03	3.86E-02
249	hsa-miR-33b*	172	115	1.50	0.40	4.27E-03	3.58E-02	0.743	5.67E-03	3.73E-02
27	hsa-miR-423-5p	3536	2224	1.59	0.46	5.06E-03	3.80E-02	0.743	1.04E-02	5.47E-02
251	hsa-miR-182	7424	6034	1.23	0.21	4.84E-03	3.77E-02	0.743	2.33E-02	9.21E-02

Figure 30

Set No.	Signature	SEQ-ID NO:	miRNAs	Acc
2000	ACS-NRS-1	SEQ ID NO: 257, SEQ ID NO: 261	hsa-miR-663b, hsa-miR-200b*	90,48%
2001	ACS-NRS-2	SEQ ID NO: 257, SEQ ID NO: 283	hsa-miR-663b, hsa-miR-191*	91,45%
2002	ACS-NRS-3	SEQ ID NO: 257, SEQ ID NO: 280, SEQ ID NO: 261	hsa-miR-663b, hsa-miR-634, hsa-miR-200b*	95,65%
2003	ACS-NRS-4	SEQ ID NO: 257, SEQ ID NO: 281, SEQ ID NO: 280, SEQ ID NO: 261	hsa-miR-663b, hsa-miR-144*, hsa-miR-634, hsa-miR-200b*	96,10%
2004	ACS-NRS-5	SEQ ID NO: 257, SEQ ID NO: 280, SEQ ID NO: 261	hsa-miR-663b, hsa-miR-634, hsa-miR-200b*	96,33%
2005	ACS-NRS-6	SEQ ID NO: 257, SEQ ID NO: 281, SEQ ID NO: 280, SEQ ID NO: 261, SEQ ID NO: 159, SEQ ID NO: 282	hsa-miR-663b, hsa-miR-144*, hsa-miR-634, hsa-miR-200b*, hsa-miR-126*, hsa-miR-519d	97,00%
2006	ACS-NRS-7	SEQ ID NO: 257, SEQ ID NO: 280, SEQ ID NO: 261, SEQ ID NO: 282	hsa-miR-663b, hsa-miR-634, hsa-miR-200b*, hsa-miR-519d	97,30%
2007	ACS-NRS-8	SEQ ID NO: 257, SEQ ID NO: 280, SEQ ID NO: 261, SEQ ID NO: 159, SEQ ID NO: 282	hsa-miR-663b, hsa-miR-634, hsa-miR-200b*, hsa-miR-126*, hsa-miR-519d	97,35%
2008	ACS-NRS-9	SEQ ID NO: 257, SEQ ID NO: 280, SEQ ID NO: 261, SEQ ID NO: 159, SEQ ID NO: 282	hsa-miR-663b, hsa-miR-634, hsa-miR-200b*, hsa-miR-126*, hsa-miR-519d	97,78%
2009	ACS-NRS-10	SEQ ID NO: 257, SEQ ID NO: 19, SEQ ID NO: 280, SEQ ID NO: 261, SEQ ID NO: 159, SEQ ID NO: 282	hsa-miR-663b, hsa-miR-767-5p, hsa-miR-634, hsa-miR-200b*, hsa-miR-126*, hsa-miR-519d	98,48%
2010	ACS-NRS-11	SEQ ID NO: 257, SEQ ID NO: 281, SEQ ID NO: 280, SEQ ID NO: 55, SEQ ID NO: 261, SEQ ID NO: 159, SEQ ID NO: 282	hsa-miR-663b, hsa-miR-144*, hsa-miR-634, hsa-miR-30e*, hsa-miR-200b*, hsa-miR-126*, hsa-miR-519d	99,33%
2011	ACS-NRS-12	SEQ ID NO: 257, SEQ ID NO: 281, SEQ ID NO: 280, SEQ ID NO: 55, SEQ ID NO: 261, SEQ ID NO: 159, SEQ ID NO: 282	hsa-miR-663b, hsa-miR-144*, hsa-miR-634, hsa-miR-30e*, hsa-miR-200b*, hsa-miR-126*, hsa-miR-519d	99,53%



EUROPEAN SEARCH REPORT

Application Number
EP 14 17 4637

5

10

15

20

25

30

35

40

45

50

55

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	AI J ET AL: "Circulating microRNA-1 as a potential novel biomarker for acute myocardial infarction", BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 391, no. 1, 1 January 2010 (2010-01-01), pages 73-77, XP026907859, ACADEMIC PRESS INC. ORLANDO, FL, US ISSN: 0006-291X, DOI: 10.1016/J.BBRC.2009.11.005 [retrieved on 2009-11-05] * abstract *	1-15	INV. C12Q1/6883
A	----- WANG GUO-KUN ET AL: "Circulating microRNA: a novel potential biomarker for early diagnosis of acute myocardial infarction in humans.", EUROPEAN HEART JOURNAL, vol. 31, no. 6, March 2010 (2010-03), pages 659-666, XP002586116, ISSN: 1522-9645 * abstract *	1-15	TECHNICAL FIELDS SEARCHED (IPC) C12Q
A	----- HOEKSTRA MENNO ET AL: "The peripheral blood mononuclear cell microRNA signature of coronary artery disease", BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 394, no. 3, 15 March 2010 (2010-03-15), pages 792-797, XP002586117, * abstract *	1-15	
----- -/--			
2 ~~The present search report has been drawn up for all claims~~			
Place of search The Hague		Date of completion of the search 13 February 2015	Examiner Aslund, Fredrik
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

EPO FORM 1503 03.02 (P04C01)



EUROPEAN SEARCH REPORT

Application Number
EP 14 17 4637

5

10

15

20

25

30

35

40

45

50

55

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	TIJSEN ANKE J ET AL: "MiR423-5p as a circulating biomarker for heart failure.", CIRCULATION RESEARCH, vol. 106, no. 6, 2 April 2010 (2010-04-02), pages 1035-1039, XP002586118, ISSN: 1524-4571 * abstract * * Supplementary data Table 1; page 1036, column 1, paragraph 2 * & Tijssen et al.: "Supplement material", Circulation Research, 2 April 2010 (2010-04-02), Retrieved from the Internet: URL:http://circres.ahajournals.org/cgi/data/CIRCRESAHA.110.218297/DC1/1 [retrieved on 2010-06-08] * page 9; table 1 *	1-15	
A	WO 2009/149182 A1 (UNIV TEXAS [US]; COREY DAVID R [US]; YOUNGER SCOTT T [US]) 10 December 2009 (2009-12-10) * sequence 20020 * -& DATABASE EMBL [Online] 14 January 2010 (2010-01-14), "Sequence 20020 from Patent W02009149182.", XP002637609, retrieved from EBI accession no. EMBL:HC275573 Database accession no. HC275573 * compound *	1-15	TECHNICAL FIELDS SEARCHED (IPC)
A	WO 2009/043353 A2 (SANTARIS PHARMA AS [DK]; OBAD SUSANNA [SE]; KAUPPINEN SAKARI [DK]; ELM) 9 April 2009 (2009-04-09) * page 93, line 35; sequence 233 * -/--	1-15	
~~The present search report has been drawn up for all claims~~			
Place of search		Date of completion of the search	Examiner
The Hague		13 February 2015	Aslund, Fredrik
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

EPO FORM 1503 03.02 (P04C01)



EUROPEAN SEARCH REPORT

Application Number
EP 14 17 4637

5

10

15

20

25

30

35

40

45

50

55

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	-& DATABASE EMBL [Online] 7 May 2009 (2009-05-07), "Sequence 233 from Patent W02009043353.", XP002637608, retrieved from EBI accession no. EMBL:GN345469 Database accession no. GN345469 * compound * ----- WO 2009/070653 A1 (UNIV OHIO STATE RES FOUND [US]; NANA-SINKHAM SERGE P [US]; MARSH CLAY) 4 June 2009 (2009-06-04) * table 2 * -----	1-15	
			TECHNICAL FIELDS SEARCHED (IPC)
~~The present search report has been drawn up for all claims~~			
Place of search		Date of completion of the search	Examiner
The Hague		13 February 2015	Aslund, Fredrik
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

EPO FORM 1503 03.02 (P04C01)



Application Number

EP 14 17 4637

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing claims for which payment was due.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☒ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

1-15(partially)

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

☐ The present supplementary European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims (Rule 164 (1) EPC).

**LACK OF UNITY OF INVENTION
SHEET B**

Application Number

EP 14 17 4637

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-15(partially)

Polynucleotides or sets of polynucleotides, methods, means, kits and miRNAs for diagnosing and/or prognosing of an acute coronary syndrome using at least the miRNA represented by seq id no: 1 (hsa-miR-1291) as a marker.

2-283. claims: 1-15(partially)

Polynucleotides or sets of polynucleotides, methods, means, kits and miRNAs for diagnosing and/or prognosing of an acute coronary syndrome using at least the miRNA represented by seq id no: 2 (hsa-miR-1283) as a marker.

[idem for each of the miRNAs represented by seq id nos: 3-283, each miRNA representing a separate invention]

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 14 17 4637

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

13-02-2015

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009149182 A1	10-12-2009	AU 2009256243 A1	10-12-2009
		CA 2726052 A1	10-12-2009
		EP 2297322 A1	23-03-2011
		US 2009326051 A1	31-12-2009
		WO 2009149182 A1	10-12-2009

WO 2009043353 A2	09-04-2009	AU 2008306327 A1	09-04-2009
		CA 2701547 A1	09-04-2009
		CN 101821391 A	01-09-2010
		DK 2205737 T3	21-05-2013
		EA 201070421 A1	29-10-2010
		EP 2203559 A2	07-07-2010
		EP 2205737 A2	14-07-2010
		EP 2623598 A1	07-08-2013
		EP 2623599 A1	07-08-2013
		ES 2406686 T3	07-06-2013
		ES 2463665 T3	28-05-2014
		JP 2010539959 A	24-12-2010
		KR 20100100774 A	15-09-2010
		NZ 583677 A	29-06-2012
		US 2009143326 A1	04-06-2009
		US 2010280099 A1	04-11-2010
		US 2010298410 A1	25-11-2010
		WO 2009043353 A2	09-04-2009
		WO 2009043354 A2	09-04-2009

WO 2009070653 A1	04-06-2009	AU 2008329755 A1	04-06-2009
		CA 2707157 A1	04-06-2009
		CN 101918594 A	15-12-2010
		EP 2225396 A1	08-09-2010
		JP 2011505143 A	24-02-2011
		US 2010323357 A1	23-12-2010
		WO 2009070653 A1	04-06-2009

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Non-patent literature cited in the description

- **Al.** *Biochem. and Biophysical Research Communication*, 2010, vol. 391, 73-77 [0004]
- **WANG et al.** *European Heart Journal*, 2010, vol. 31, 659-666 [0004]
- A multilingual glossary of biotechnological terms: (IUPAC Recommendations). Helvetica Chimica Acta, 1995 [0014]
- Molecular Cloning: A Laboratory Manual. Cold Spring Harbor Laboratory Press, 1989 [0015]
- **PT NELSON et al.** *Nature methods*, 2004, vol. 1 (2), 1 [0276]
- **VORWERK S. et al.** Microfluidic based enzymatic on-chip labeling of miRNAs. *N. Biotechnol.*, 20 August 2008, vol. 25 (2-3), 142-9 [0276]
- **ZHAO Y ; SAMAL E ; SRIVASTAVA D.** Serum response factor regulates a muscle-specific microRNA that targets Hand2 during cardiogenesis. *Nature*, 2005, vol. 436, 214-20 [0314]
- **DRESIOS J ; ASCHRAFI A ; OWENS GC ; VANDERKLISH PW ; EDELMAN GM ; MAURO VP.** Cold stress-induced protein Rbm3 binds 60S ribosomal subunits, alters microRNA levels, and enhances global protein synthesis. *Proc Natl Acad Sci USA.*, 2005, vol. 102, 1865-70 [0314]
- **XU P ; VERNOOY SY ; GUO M ; HAY BA.** The *Drosophila* microRNA Mir-14 suppresses cell death and is required for normal fat metabolism. *Curr Biol.*, 2003, vol. 13, 790-5 [0314]
- **CIMMINO A ; CALIN GA ; FABBRI M ; IORIO MV ; FERRACIN M ; SHIMIZU M ; WOJCIK SE ; AQEILAN RI ; ZUPO S ; DONO M.** miR-15 and miR-16 induce apoptosis by targeting BCL2. *Proc Natl Acad Sci U S A.*, 2005, vol. 102, 13944-9 [0314]
- **CALIN GA ; GARZON R ; CIMMINO A ; FABBRI M ; CROCE CM.** MicroRNAs and leukemias: how strong is the connection?. *Leuk Res.*, 2006, vol. 30, 653-5 [0314]
- **CALIN GA ; FERRACIN M ; CIMMINO A ; DI LEVA G ; SHIMIZU M ; WOJCIK SE ; IORIO MV ; VISIONE R ; SEVER NI ; FABBRI M.** A MicroRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. *N Engl J Med.*, 2005, vol. 353, 1793-801 [0314]
- **LEE RC ; FEINBAUM RL ; AMBROS V.** The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell.*, 1993, vol. 75, 843-54 [0314]
- **DONG S ; CHENG Y ; YANG J ; LI J ; LIU X ; WANG X ; WANG D ; KRALL TJ ; DELPHIN ES ; ZHANG C.** MicroRNA expression signature and the role of microRNA-21 in the early phase of acute myocardial infarction. *J Biol Chem.*, 2009, vol. 284, 29514-25 [0314]
- **CAI B ; PAN Z ; LU Y.** The Roles of MicroRNAs in Heart Diseases: A Novel Important Regulator. *Curr Med Chem.*, 2009 [0314]
- **NEWTON PJ ; BETIHAVAS V ; MACDONALD P.** The role of b-type natriuretic peptide in heart failure management. *Aust Crit Care*, 2009, vol. 22, 117-23 [0314]
- **LAINSCAK M ; ANKER MS ; VON HAEHLING S ; ANKER SD.** Biomarkers for chronic heart failure : diagnostic, prognostic, and therapeutic challenges. *Herz*, 2009, vol. 34, 589-93 [0314]
- **MANZANO-FERNANDEZ S ; BORONAT-GARCIA M ; ALBALADEJO-OTON MD ; PASTOR P ; GARRIDO IP ; PASTOR-PEREZ FJ ; MARTINEZ-HERNANDEZ P ; VALDES M ; PASCUAL-FIGAL DA.** Complementary prognostic value of cystatin C, N-terminal pro-B-type natriuretic Peptide and cardiac troponin T in patients with acute heart failure. *Am J Cardiol.*, 2009, vol. 103, 1753-9 [0314]
- **KATUS HA ; REMPPIS A ; LOOSER S ; HALLERMEIER K ; SCHEFFOLD T ; KUBLER W.** Enzyme linked immuno assay of cardiac troponin T for the detection of acute myocardial infarction in patients. *J Mol Cell Cardiol.*, 1989, vol. 21, 1349-53 [0314]
- **MUKOYAMA M ; NAKAO K ; SAITO Y ; OGAWA Y ; HOSODA K ; SUGA S ; SHIRAKAMI G ; JOUGASAKI M ; IMURA H.** Increased human brain natriuretic peptide in congestive heart failure. *N Engl J Med.*, 1990, vol. 323, 757-8 [0314]
- **GERSZTEN RE ; WANG TJ.** The search for new cardiovascular biomarkers. *Nature*, 2008, vol. 451, 949-52 [0314]
- **GALLEGO-DELGADO J ; LAZARO A ; OSENDE JI ; BARDERAS MG ; BLANCO-COLIO LM ; DURAN MC ; MARTIN-VENTURA JL ; VIVANCO F ; EGIDO J.** Proteomic approach in the search of new cardiovascular biomarkers. *Kidney Int Suppl.*, 2005, 103-7 [0314]
- **GIANNITSIS E ; ROTH HJ ; LEITHAUSER RM ; SCHERHAG J ; BENEKE R ; KATUS HA.** New highly sensitivity assay used to measure cardiac troponin T concentration changes during a continuous 216-km marathon. *Clin Chem.*, 2009, vol. 55, 590-2 [0314]

- **GRIFFITHS-JONES S.** miRBase: the microRNA sequence database. *Methods Mol Biol.*, 2006, vol. 342, 129-38 [0314]
- **VORWERK S ; GANTER K ; CHENG Y ; HOHEISEL J ; STAHLER PF ; BEIER M.** Microfluidic-based enzymatic on-chip labeling of miRNAs. *N Biotechnol.*, 2008, vol. 25, 142-9 [0314]
- **BENJAMINI Y ; HOCHBERG Y.** Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Statist Soc B.*, 1995, vol. 57, 289-300 [0314]
- **MEDER B ; KATUS HA ; ROTTBAUER W.** Right into the heart of microRNA-133a. *Genes Dev.*, 2008, vol. 22, 3227-31 [0314]
- **THUM T ; GROSS C ; FIEDLER J ; FISCHER T ; KISSLER S ; BUSSEN M ; GALUPPO P ; JUST S ; ROTTBAUER W ; FRANTZ S.** MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. *Nature*, 2008, vol. 456, 980-4 [0314]
- **CHEN X ; BA Y ; MA L ; CAI X ; YIN Y ; WANG K ; GUO J ; ZHANG Y ; CHEN J ; GUO X.** Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. *Cell Res.*, 2008, vol. 18, 997-1006 [0314]
- **AI J ; ZHANG R ; LI Y ; PU J ; LU Y ; JIAO J ; LI K ; YU B ; LI Z ; WANG R.** Circulating microRNA-1 as a potential novel biomarker for acute myocardial infarction. *Biochem Biophys Res Commun.*, 2009 [0314]
- Risk stratification and survival after myocardial infarction. *N Engl J Med.*, 1983, vol. 309, 331-6 [0314]
- **ROTTBAUER W ; GRETEN T ; MULLER-BARBORFF M ; REMPPIS A ; ZEHELEIN J ; GRUNIG E ; KATUS HA.** Troponin T: a diagnostic marker for myocardial infarction and minor cardiac cell damage. *Eur Heart J.*, 1996, vol. 17, 3-8 [0314]
- **KURZ K ; SCHILD C ; ISFORT P ; KATUS HA ; GIANNITSIS E.** Serial and single time-point measurements of cardiac troponin T for prediction of clinical outcomes in patients with acute ST-segment elevation myocardial infarction. *Clin Res Cardiol.*, 2009, vol. 98, 94-100 [0314]
- **TZIVONI D ; KOUKOU D ; GUETTA V ; NOVACK L ; COWING G.** Comparison of Troponin T to creatine kinase and to radionuclide cardiac imaging infarct size in patients with ST-elevation myocardial infarction undergoing primary angioplasty. *Am J Cardiol.*, 2008, vol. 101, 753-7 [0314]
- **DUISTERS RF ; TIJSEN AJ ; SCHROEN B ; LEENDERS JJ ; LENTINK V ; VAN DER MADE I ; HERIAS V ; VAN LEEUWEN RE ; SCHELLINGS MW ; BARENBRUG P.** miR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. *Circ Res.*, 2009, vol. 104, 170-8 [0314]
- Risk stratification and survival after myocardial infarction. *N Engl J Med*, 1983, vol. 309, 331-336 [0314]
- **ADACHI T ; NAKANISHI M ; OTSUKA Y ; NISHIMURA K ; HIROKAWA G ; GOTO Y ; NONOGI H ; IWAIN.** Plasma microRNA 499 as a biomarker of acute myocardial infarction. *Clin Chem*, 2010, vol. 56, 1183-1185 [0314]
- **AI J ; ZHANG R ; LI Y ; PU J ; LU Y ; JIAO J ; LI K ; YU B ; LI Z ; WANG R.** Circulating microRNA-1 as a potential novel biomarker for acute myocardial infarction. *Biochem Biophys Res Commun*, 2010, vol. 391, 73-77 [0314]
- **ALIFERIS CF ; STATNIKOV A ; TSAMARDINOS I ; SCHILDCROUT JS ; SHEPHERD BE ; HARRELL FE, JR.** Factors influencing the statistical power of complex data analysis protocols for molecular signature development from microarray data. *PLoS ONE*, 2009, vol. 4, e4922 [0314]
- **BENJAMINI Y ; HOCHBERG Y.** Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Statist Soc B*, 1995, vol. 57, 289-300 [0314]
- **BOSE D ; VON BIRGELEN C ; ZHOU XY ; SCHMERMUNDA ; PHILIPPS ; SACKS ; KONORZA T ; MOHLENKAMP S ; LEINWEBER K ; KLEINBONGARD P.** Impact of atherosclerotic plaque composition on coronary microembolization during percutaneous coronary interventions. *Basic Res Cardiol*, 2008, vol. 103, 587-597 [0314]
- **CAI B ; PAN Z ; LU Y.** The roles of microRNAs in heart diseases: a novel important regulator. *Curr Med Chem*, 2010, vol. 17, 407-411 [0314]
- **CHEN X ; BA Y ; MA L ; CAI X ; YIN Y ; WANG K ; GUO J ; ZHANG Y ; CHEN J ; GUO X.** Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. *Cell Res*, 2008, vol. 18, 997-1006 [0314]
- **CIMMINO A ; CALIN GA ; FABBRI M ; IORIO MV ; FERRACIN M ; SHIMIZU M ; WOJCIK SE ; AQEILAN RI ; ZUPO S ; DONO M.** miR-15 and miR-16 induce apoptosis by targeting BCL2. *Proc Natl Acad Sci U S A*, 2005, vol. 102, 13944-13949 [0314]
- **D'ALESSANDRA Y ; DEVANNA P ; LIMANA F ; STRAINO S ; DI CARLO A ; BRAMBILLA PG ; RUBINO M ; CARENA MC ; SPAZZAFUMO L ; DE SIMONE M.** Circulating microRNAs are new and sensitive biomarkers of myocardial infarction. *Eur Heart J*, 09 June 2010 [0314]
- **DONG S ; CHENG Y ; YANG J ; LI J ; LIU X ; WANG X ; WANG D ; KRALL TJ ; DELPHIN ES ; ZHANG C.** MicroRNA expression signature and the role of microRNA-21 in the early phase of acute myocardial infarction. *J Biol Chem*, 2009, vol. 284, 29514-29525 [0314]
- **DRESIOS J ; ASCHRAFI A ; OWENS GC ; VANDERKLISH PW ; EDELMAN GM ; MAURO VP.** Cold stress-induced protein Rbm3 binds 60S ribosomal subunits, alters microRNA levels, and enhances global protein synthesis. *Proc Natl Acad Sci USA*, 2005, vol. 102, 1865-1870 [0314]

- **DUISTERS RF ; TIJSEN AJ ; SCHROEN B ; LEENDERS JJ ; LENTINK V ; VAN DER MADE I ; HERIAS V ; VAN LEEUWEN RE ; SCHELLINGS MW ; BARENBRUG P.** miR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. *Circ Res*, 2009, vol. 104, 170-178 [0314]
- **FLEISSNER F ; JAZBUTYTE V ; FIEDLER J ; GUPTA SK ; YIN X ; XU Q ; GALUPPO P ; KNEITZ S ; MAYR M ; ERTL G.** Short communication: asymmetric dimethylarginine impairs angiogenic progenitor cell function in patients with coronary artery disease through a microRNA-21-dependent mechanism. *Circ Res*, 2010, vol. 107, 138-143 [0314]
- **GALLEGO-DELGADO J ; LAZARO A ; OSENDE JI ; BARDERAS MG ; BLANCO-COLIO LM ; DURAN MC ; MARTIN-VENTURA JL ; VIVANCO F ; EGIDO J.** Proteomic approach in the search of new cardiovascular biomarkers. *Kidney Int Suppl*, 2005, 103-107 [0314]
- **GRSZTENRE ; WANG TJ.** The search for new cardiovascular biomarkers. *Nature*, 2008, vol. 451, 949-952 [0314]
- **GIANNITSIS E ; ROTH HJ ; LEITHAUSER RM ; SCHERHAG J ; BENEKER ; KATUS HA.** New highly sensitivity assay used to measure cardiac troponin T concentration changes during a continuous 216-km marathon. *Clin Chem*, 2009, vol. 55, 590-592 [0314]
- **GRIFFITHS-JONES S.** miRBase: the microRNA sequence database. *Methods Mol Biol*, 2006, vol. 342, 129-138 [0314]
- **HOCHBERG Y.** A sharper bonferroni procedure for multiple tests of significance. *Biometrika*, 1988, vol. 75, 185-193 [0314]
- **HOEKSTRA M ; VAN DER LANS CA ; HALVORSEN B ; GULLESTAD L ; KUIPER J ; AUKRUST P ; VAN BERKEL TJ ; BIESSEN EA.** The peripheral blood mononuclear cell microRNA signature of coronary artery disease. *Biochem Biophys Res Commun*, 2010, vol. 394, 792-797 [0314]
- **JENNEWEIN C ; VON KNETHEN A ; SCHMID T ; BRUNE B.** MicroRNA-27b contributes to lipopolysaccharide-mediated peroxisome proliferator-activated receptor gamma (PPARgamma) mRNA destabilization. *J Biol Chem*, 2010, vol. 285, 11846-11853 [0314]
- **KATUS HA ; REMPPIS A ; LOOSER S ; HALLERMEIER K ; SCHEFFOLD T ; KUBLER W.** Enzyme linked immuno assay of cardiac troponin T for the detection of acute myocardial infarction in patients. *J Mol Cell Cardiol*, 1989, vol. 21, 1349-1353 [0314]
- **KONSTANDIN MH ; AKSOY H ; WABNITZ GH ; VOLZ C ; ERBEL C ; KIRCHGESSNER H ; GIANNITSIS E ; KATUS HA ; SAMSTAG Y ; DENGLER TJ.** Beta2-integrin activation on T cell subsets is an independent prognostic factor in unstable angina pectoris. *Basic Res Cardiol*, 2009, vol. 104, 341-351 [0314]
- **KURZ K ; SCHILD C ; ISFORT P ; KATUS HA ; GIANNITSIS E.** Serial and single time-point measurements of cardiac troponin T for prediction of clinical outcomes in patients with acute ST-segment elevation myocardial infarction. *Clin Res Cardiol*, 2009, vol. 98, 94-100 [0314]
- **LAINSCAK M ; ANKER MS ; VON HAEHLING S ; ANKER SD.** Biomarkers for chronic heart failure : diagnostic, prognostic, and therapeutic challenges. *Herz*, 2009, vol. 34, 589-593 [0314]
- **LEE RC ; FEINBAUM RL ; AMBROS V.** The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell*, 1993, vol. 75, 843-854 [0314]
- **LEIDINGER P ; KELLER A ; BORRIES A ; REICHRATH J ; RASS K ; JAGER SU ; LENHOF HP ; MEESE E.** High-throughput miRNA profiling of human melanoma blood samples. *BMC Cancer*, 2010, vol. 10, 262 [0314]
- **MANZANO-FERNANDEZ S ; BORONAT-GARCIA M ; ALBALADEJO-OTON MD ; PASTOR P ; GARRIDO IP ; PASTOR-PEREZ FJ ; MARTINEZ-HERNANDEZ P ; VALDES M ; PASCUAL-FIGAL DA.** Complementary prognostic value of cystatin C, N-terminal pro-B-type natriuretic Peptide and cardiac troponin T in patients with acute heart failure. *Am J Cardiol*, 2009, vol. 103, 1753-1759 [0314]
- **MEDERB ; KATUS HA ; ROTTBAUER W.** Right into the heart of microRNA-133a. *Genes Dev*, 2008, vol. 22, 3227-3231 [0314]
- **MEREDITH D ; PANCHATCHARAM M ; MIRIYALA S ; TSAI YS ; MORRIS AJ ; MAEDA N ; STOUFFER GA ; SMYTH SS.** Dominant-negative loss of PPAR-gamma function enhances smooth muscle cell proliferation, migration, and vascular remodeling. *Arterioscler Thromb Vasc Biol*, 2009, vol. 29, 465-471 [0314]
- **MUKOYAMA M ; NAKAO K ; SAITO Y ; OGAWA Y ; HOSODA K ; SUGA S ; SHIRAKAMI G ; JOUGASAKI M ; IMURA H.** Increased human brain natriuretic peptide in congestive heart failure. *N Engl J Med*, 1990, vol. 323, 757-758 [0314]
- **NEWTON PJ ; BETIHAVAS V ; MACDONALD P.** The role of b-type natriuretic peptide in heart failure management. *Aust Crit Care*, 2009, vol. 22, 117-123 [0314]
- **PORELA P ; PULKKI K ; VOIPIO-PULKKI LM ; PETTERSSON K ; LEPPANEN V ; NEVALAINEN TJ.** Level of circulating phospholipase A2 in prediction of the prognosis of patients with suspected myocardial infarction. *Basic Res Cardiol*, 2000, vol. 95, 413-417 [0314]
- **ROTTBAUER W ; GRETEN T ; MULLER-BARDORFF M ; REMPPIS A ; ZEHELEIN J ; GRUNIG E ; KATUS HA.** Troponin T: a diagnostic marker for myocardial infarction and minor cardiac cell damage. *Eur Heart J*, 1996, vol. 17, 3-8 [0314]

- Team-RDC (2008) R: A Language and Environment for Statistical Computing. *R Foundation for Statistical Computing*, 2008 [0314]
- THUM T ; GROSS C ; FIEDLER J ; FISCHER T ; KISSLER S ; BUSSEN M ; GALUPPO P ; JUST S ; ROTTBAUER W ; FRANTZ S. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. *Nature*, 2008, vol. 456, 980-984 [0314]
- TZIVONI D ; KOUKOU D ; GUETTA V ; NOVACK L ; COWING G. Comparison of Troponin T to creatine kinase and to radionuclide cardiac imaging infarct size in patients with ST-elevation myocardial infarction undergoing primary angioplasty. *Am J Cardiol*, 2008, vol. 101, 753-757 [0314]
- VOELLENKLE C ; VAN ROOIJ J ; CAPPUZZELLO C ; GRECO S ; ARCELLI D ; DI VITO L ; MELILLO G ; RIGOLINI R ; COSTA E ; CREA F. MicroRNA signatures in peripheral blood mononuclear cells of chronic heart failure patients. *Physiol Genomics*, 2010, vol. 42, 420-426 [0314]
- VORWERK S ; GANTER K ; CHENG Y ; HOHEISEL J ; STAHLER PF ; BEIER M. Microfluidic-based enzymatic on-chip labeling of miRNAs. *N Biotechnol*, 2008, vol. 25, 142-149 [0314]
- WANG GK ; ZHU JQ ; ZHANG JT ; LI Q ; LI Y ; HE J ; QIN YW ; JING Q. Circulating microRNA: a novel potential biomarker for early diagnosis of acute myocardial infarction in humans. *Eur Heart J*, 2010, vol. 31, 659-666 [0314]
- XIN M ; SMALL EM ; SUTHERLAND LB ; QI X ; MCANALLY J ; PLATO CF ; RICHARDSON JA ; BASSEL-DUBY R ; OLSON EN. MicroRNAs miR-143 and miR-145 modulate cytoskeletal dynamics and responsiveness of smooth muscle cells to injury. *Genes Dev*, 2009, vol. 23, 2166-2178 [0314]
- XU P ; VERNOOY SY ; GUO M ; HAY BA. The Drosophila microRNA Mir-14 suppresses cell death and is required for normal fat metabolism. *Curr Biol*, 2003, vol. 13, 790-795 [0314]
- ZHAO Y ; SAMAL E ; SRIVASTAVA D. Serum response factor regulates a muscle-specific microRNA that targets Hand2 during cardiogenesis. *Nature*, 2005, vol. 436, 214-220 [0314]